Universidade de Aveiro Departamento de Ciências Médicas
Ano 2016

RICARDO DANIEL DA CONCEIÇÃO SILVA

O COORDENADOR DE INVESTIGAÇÃO CLÍNICA: A COORDENAÇÃO DE UM ENSAIO CLÍNICO NUMA DOENÇA RARA

THE CLINICAL RESEARCH COORDINATOR: THE COORDINATION OF A CLINICAL TRIAL IN A RARE DISEASE

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Projeto apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor Bruno Gago, Professor Auxiliar Convidado do Departamento de Ciências Médicas da Universidade de Aveiro

Quero dedicar este projeto à minha família, orientadores, equipa de investigação da Unidade Corino de Andrade e a todos os doentes que tive a oportunidade de conhecer durante a realização deste projeto

o júri

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agradecimentos

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palavras-chave

Coordenador de Investigação Clínica, Ensaio Clínico, Investigação e Desenvolvimento Farmacêutico, Doença Rara, Experiência Profissional, Biomedicina Farmacêutica.

resumo

A presente tese tem como principal objetivo descrever a atividade profissional de um coordenador de investigação clínica. Mais especificamente, pretende demonstrar a importância deste profissional no contexto do desenvolvimento de novos fármacos através da coordenação de um ensaio clínico numa doença rara em contexto hospitalar.

Neste sentido, será abordado o processo de desenvolvimento de novos fármacos e discutido o atual paradigma de investigação e desenvolvimento farmacêutico. Também será analisada a realidade portuguesa dos ensaios clínicos e o desenvolvimento de novos medicamentos em doenças raras.

Finalmente, será descrita de forma detalhada a implementação de um ensaio clínico na perspetiva de um coordenador de investigação clínica e realçada a importância do mestrado em Biomedicina Farmacêutica na atividade profissional de um coordenador de investigação clínica.

keywords

Clinical Research Coordinator, Clinical Trial, Pharmaceutical Research and Development, Rare Disease, Professional Experience, Pharmaceutical Medicine.

abstract

This thesis aims to describe the professional activity of a clinical research coordinator. More specifically, it intends to demonstrate the importance of its role in the context of new drug development through the example of the coordination of a clinical trial in a rare disease in a hospital.
For this purpose, the drug development process will be addressed and it will also be discussed the current pharmaceutical research and development paradigm. The Portuguese clinical trial reality and development of new drugs for rare diseases will also be scrutinised. Finally, the implementation of a clinical trial from the perspective of a clinical research coordinator will be described in detail and the importance of the Pharmaceutical Medicine Master in the professional activity of a clinical research coordinator will be highlighted.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
AMP	Accelerating Medicines Partnership
AUC	Area Under the Curve
CDP	Clinical Development Plan
CMPH	Committee for Medicinal Products for Human Use
CHP	Centro Hospitalar do Porto
CIOMS	Council for International Organizations for Medical Sciences
COMP	Committee for Orphan Medicinal Products
CRC	Clinical Research Coordinator
CPI	Critical Path Initiative
CNPD	Comissão Nacional de Proteção de Dados (National Committee for Data Protection)
CRA	Clinical Research Associate
CEIC	Comissão de Ética para a Investigação Clínica (Portuguese Ethics Committee for Clinical Research)
CRO	Contract Research Organization
CRF	Case Report Form
CSDD	Center for the Study of Drug Development
CTD	Common Technical Document
CV	Curriculum Vitae
DEFI	Departamento de Ensino, Formação e Investigação (Department of Education, Training and Research)
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
EEA	European Economic Area
FAP	Familial Amyloid Polyneuropathy
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMP	Good Manufacturing Practice
HSA	Hospital de Santo António
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation - Good Clinical Practices
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (National Authority of Medicines and Health Products, IP)
IVRS/IWRS	Interactive Voice/Web Response System
ISF	Investigator Site File
IRB/IEC	Institutional Review Board / Independent Ethic Committee
MAA	Marketing Authorization Application

NCA	National Competent Authorities
ODA	Orphan Drug Act
PhIRD-SD	Pharmaceutical Industry Research & Development Slow Down
PASS	Post-Authorization Safety Study
PI	Principal Investigator
R&D	Research and Development
RD	Rare Disease
RNCES	Rede Nacional de Comissões de Ética para a Saúde (National Network of Ethics Committee for Health)
RNEC	Rede Nacional de Estudos Clínicos (National Register of Clinical Trials)
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TTR	Transthyretin
UCA	Unidade Corino de Andrade
UCP	Unidade Clínica de Paramiloidose
USA	United States of America

1. Introduction

When I started working as a Clinical Research Coordinator (CRC) eight years ago I had no idea of how a drug was discovered, developed and brought to the market. At the same time, I had a very limited comprehension of the profession I was about to embrace and the importance that it had in the context of Pharmaceutical Research and Development (R&D). However, there came a time when I decided to take a step forward in my education and apply to the Master in Pharmaceutical Medicine of the University of Aveiro. This was a decisive moment that revealed to be very important at a formative and professional level. By the time I had to make a decision on my master thesis format, it seemed obvious to me that the Project modality would be the most suitable and at the same time the most challenging option. After the Pharmaceutical Training Program curricular component, I was in possession of the necessary knowledge to make a profound reflection on my professional experience as a CRC and to demonstrate, with the adoption of the appropriate methodologies, how that knowledge could be applied in a practical situation within an organizational setting. Besides, by choosing this modality I had an excellent opportunity to improve my daily practice.

The main goal of this project is to demonstrate how a phase 2/3 clinical trial with an orphan drug that is currently undergoing in a hospital can be implemented and coordinated.

I will begin by addressing the state-of-art in terms of the drug development process, outlining the main stages that a drug undergoes from discovery to post-marketing phases, with particular emphasis on drug development stage, and more specifically on clinical trials. Because the context is very relevant I have chosen to address the current R&D paradigm by analyzing its mains challenges and opportunities. In the third chapter, I will characterize the clinical trial activity in Portugal, focusing on what are the main constraints and what could be done to overcome the diagnosed difficulties and bring Portugal to a forefront position in terms of clinical research.

Because the project that it is being implemented is related with the treatment of a rare and severe disease, chapter four will focus on unmet medical needs, particularly in orphan drugs and clinical trials in orphan drugs.

The CRC role will be characterized in a detailed way on chapter five and on chapter six I will demonstrate how a clinical trial is implemented and coordinated in a hospital setting. For that, I will characterize the investigative site, the target disease, the Investigational Medicinal Product (IMP) and the clinical trial. Concomitantly, I will outline and explain the three main stages of a clinical trial at the investigative site, namely, trial preparation, conduct and close-out.

Finally, I will discuss my experience throughout the development of this project by trying to demonstrate what have been the most relevant learnings, challenges, opportunities and pointing some personal perspectives for the future.

I sincerely hope this project can serve as useful guide for all of those who wish to know more about clinical research coordination.

2. State-of-the-Art

2.1. The Drug Development Process

Researching and developing new drugs is a long and highly regulated process that involves a significant risk of failure. It is unequivocal that discovering new and innovative medicines carries with it a number of advantages for patients and health care systems. They are reflected in the decrease in hospitalization rates, in the fewer secondary effects associated with medicines, in the significant improvement of patient's quality of life and also in its increased productivity levels and longevity. However, there is evidence that this activity is growing in terms of complexity, length and costs. It is widely acknowledged that it takes between 10 to 15 years and an estimate cost of about 2.6 billion dollars to research and develop a new drug with success. Surprisingly, the probability of clinical success (that is defined as the chance for a drug to be approved to enter clinical testing) is lower than 12% (1-6).

To better understand this process, we will now outline and characterize the several stages inherent to the drug research and development process:

2.1.1. Basic Research and Drug Discovery

These early stages of research are set to identify an investigational drug and to perform the primary tests in laboratories. At this level, researchers will explore the genetic basis of a disease or the microstructure of a receptor/enzyme active site with the goal of developing molecules capable to perform specific interactions and potential therapeutic outcomes. Thousands of compounds are potential candidates, however, only a few will demonstrate to be promising and call for subsequent study (1, 3, 5, 7, 8).This first stage includes:

- **Pre-discovery:** Advances in molecular medicine and computational tools are allowing a better and more profound knowledge of diseases. At this stage, it is important to understand the condition or disease for which a new drug is going to be developed (1).
- **Target Identification and validation:** A drug target can be defined as a molecular structure in the body with the potential to interact with a drug compound and likely

produce a clinical effect. At this point, investigators will perform studies using cells, tissues and animal models to understand if that specific target can be influenced by the drug (1, 3, 7, 8).

- **Drug Discovery:** After a good understanding of the disease pathway and target identification, investigators will put their focus on narrowing the number of compounds to one lead compound with the potential to become a medicine. Many techniques are used and they can range from high-throughput techniques to the use of advanced biotechnology to genetically engineer living systems (1, 3, 5, 8).
- **Early safety testing:** Concerns with safety are continuous and shown across the entire drug development process, starting long before the drug reaches humans. By using living cells, animals and/or computational models, investigators will try to assess the preliminary pharmacokinetics and pharmacodynamics of the investigational drug (1, 3, 5).
- **Lead Optimization:** The compounds that have survived screening will need to be optimized. Throughout this process, investigators will alter some of their properties in order to improve their safety and efficacy. Hundreds of tests are performed and will luckily lead to one or more compounds that will pass to subsequent stages (1, 3, 5).

2.1.2. Non-Clinical Testing

Before clinical phases, which involve human beings, it is mandatory to conduct several non-clinical studies in order to gather evidence that the compound is potentially safe to be tested in humans(9). As stated by International Conference on Harmonisation (ICH) Topic E 8 – General Considerations for clinical Trials: “Before any clinical trial is carried out, results of non-clinical investigations or previous human studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in humans” (10).

Non-clinical testing, that consists of *in vivo* and *in vitro* studies, is focused on collecting data and relevant information that will ensure humans won’t be exposed to unreasonable risk during early stages of clinical development. They can be divided into three specific areas: Pharmacological, Pharmacokinetics and Toxicological studies (11).

The pharmacological studies, usually divided into primary pharmacodynamics, secondary pharmacodynamics and safety pharmacology studies, are essential to determine proof of principle, dosing schedules/dose-escalation methods, guidance for selecting the appropriate test species and for the selection of the start dose for first administration in humans (12, 13).

Pharmacokinetics parameters on the animal species must be available before phase I studies. These include peak plasma/serum levels, area under the curve (AUC) and half-life. Regulatory guidance indicates that Pharmacokinetic data should be demonstrated in two species prior to the first dose in humans (13).

In what concerns toxicology studies, they are conducted with the purpose of determining the chemical substance degree of toxicity, the relationship between dose and adverse effects and also to give information on target functions and organs with the goal to provide meaningful assessment of the data obtained. This will allow for a scientifically supported extrapolation of the potential effects expected in the human situation. As ICH guideline M3 [R2] states: “The non-clinical safety study recommendations for the marketing approval of a pharmaceutical usually include single and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance studies and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Other non-clinical studies include pharmacology studies for safety assessment (safety pharmacology) and pharmacokinetic studies”(14).

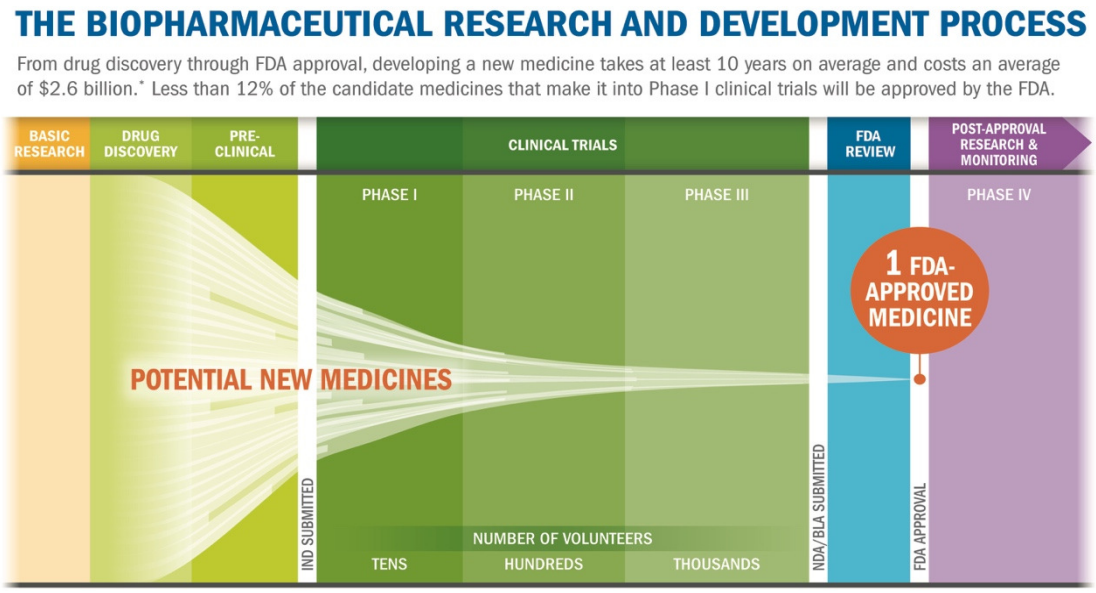

Figure 1 - The Biopharmaceutical Research and Development Process (adapted from (1))

2.1.3. Clinical Development

Clinical development starts after submission of the clinical trial to competent authorities. Only after their review and authorization may the clinical trials begin. The process of trial submission to authorities will be discussed in detail in chapter 6.

2.1.3.1. Clinical Trials

Clinical Trials are scientific investigations that have the purpose to examine and evaluate the safety and efficacy of new drugs or therapeutic procedures using human beings. They represent a critical stage of new drugs development once they are currently the main source of evidence generation in what concerns delivering new medicines. Also, they constitute a fundamental research tool in the effort to develop new medicines by gathering regulatory authorities required data, whether for bringing cutting-edge new therapies or simply for product license extensions for already marketed medicines (3, 6, 15, 16).

Clinical Trials Directive (2001/20/EC) defines Clinical Trials as “any investigation in human subjects intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal product, or to identify

any adverse reactions to one or more investigational medicinal product, examine the absorption, distribution, metabolism and the elimination of one or more investigational medicinal product in order to ascertain its safety or efficacy" (17).

According to Griffin et al (5), Clinical Trials have five purposes: "To move a drug through a development programme; To gain marketing authorization; To guide treatment of individual patients; To investigate a specific property of the drug, such as incidence of an adverse event (AE); To select one drug rather than another for addition to a therapeutic formulary and inform a health policy".

Clinical trials are of major importance within the drug development process. Results deriving from clinical trials are commonly considered the highest level of evidence for determining if a certain treatment is indeed effective and safe. Also, the experimental drugs that are currently in the drug development pipeline represent a major hope and will most likely become the medicines that have the potential to drive new treatments and potential cures over the decade for a number of diseases and conditions. They range from addressing the substantial unmet medical need in diabetes and cardiovascular diseases to rare diseases for which currently there are few or no effective treatments (18, 19).

In 2013, there were approximately 6.000 ongoing clinical trials in the United States of America (USA) that involved more than 1 million participants. Also, a recent study concluded that there are more than 5.000 medicines in the drug development pipeline worldwide and that 70% of the potential medicines in development represent novel approaches to addressing disease in such areas as neurology, cancer, diabetes, and immunology. New scientific approaches representing the cutting edge of research and innovation are being explored throughout a number of different therapeutic areas in clinical trials across many countries, including new cell and gene therapies, and targeted therapies often referred to as precision medicines or personalized medicines (18).

It is widely known that clinical trials represent the higher resource consumption part of the R&D process. Because of the cost and length associated, they have an important impact and also represent a considerable investment in the communities where they are conducted by helping to create jobs and boost local economies. Beyond the recognizable

profound value to patients and society brought by new medicines and improved treatments, the major resource investments necessary to implement clinical trials, such as hiring staff and contractors, create significant value within communities (18, 19).

Studies suggest the existence of a clinical trial effect associated with institutions that are involved and conduct clinical trials that translates into better outcomes, higher adherence to guidelines and a and greater use of evidence in clinical practice (20-22).

Despite the efforts and the proven positive impact clinical trials have in society, data from the Center for the Study of Drug Development (CSDD) at Tufts University in the USA indicates that there are still many constraints, with a negative impact in clinical trial activity. They range from increasingly longer study start-up times, slowing enrollment of patients into trials, increasing clinical trials costs and a significant decline on the investigator interest to participate in clinical trials. The main reasons contributing for delays in trials are related to long and difficult budget negotiations between sponsor, investigators and institution where trials are to be conducted, long Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval times, poor patient recruitment and low retention rates and also unrealistic protocol requirements that are becoming more complex and burdensome (23).

2.1.3.2. Clinical Trial Phases

Clinical trials are divided into several distinct phases. We have chosen to use the standard classification that uses numbers to classify the several clinical stages IMP undergoes. However, we are witnessing a blurring of the boundaries between clinical phases of drug development. As a prove of this new trend, ICH has released guidelines that instead describe the different stages based on the underlying objective: Human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use (10, 24).

Phase 0

Despite relatively unknown, Phase 0 is a recent designation intended to describe exploratory studies that involve very limited human exposure to a drug, with no therapeutic or diagnostic goals. These studies main goal is to understand the cellular level

effects of a potential new drug by using an extremely low level dosing, unlikely to cause any therapeutic or adverse results (18).

Phase I

Commonly known as First-in-Human studies, Phase I clinical trials or Human Pharmacology are of particular importance, since this is the first time an IMP is given to humans. These early stage trials have nontherapeutic goals and are set to estimate tolerability and also trying to characterize Pharmacokinetics ("What the body does to the drug") and Pharmacodynamics ("What the drug does to the body")(24, 25).

Because understanding safety and pharmacokinetics is the main objective at this stage, normally they are conducted in healthy volunteers. However, when significant toxicity is expected or in cases of a narrow therapeutic index of the IMP, phase I trials can be conducted with patients (9).

Phase I studies can be quite challenging, since the compound being tested might not be available yet in the optimal formulation for the patient population of interest. Also, since at this stage the IMP has not been scaled up, the compounds can represent a major financial investment to sponsors. A constant balance of the likelihood of the drug succeeding in opposition to the resources required for the full-scale manufacturing process is essential at this point. Despite the appropriate study design is dependent on study goals, usually Phase I studies are open-label. If pharmacodynamics of efficacy measures are to be used, then blinding and inclusion of a placebo arm is necessary. Concomitantly, these trials are focused in determining the minimum and maximum doses tolerated by humans and carefully characterizing the pharmacokinetics around the dose range being tested (14, 24).

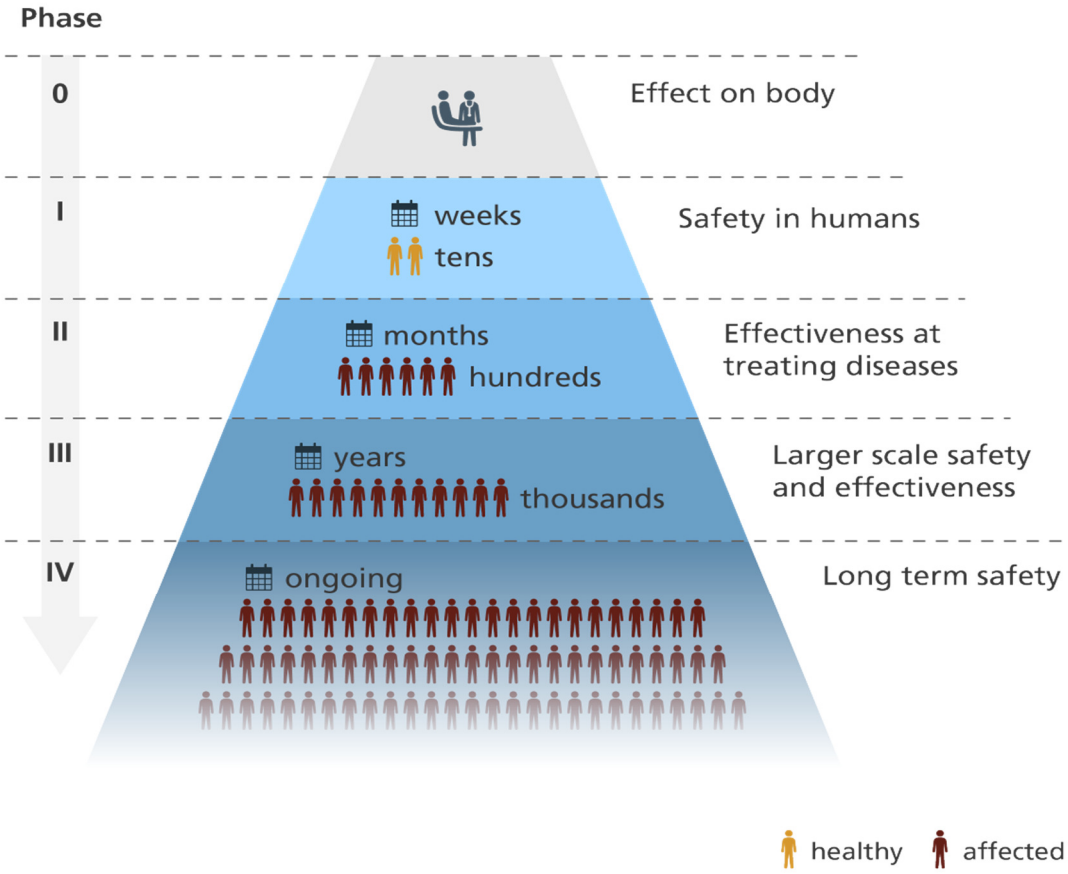

Figure 2 - Phases in clinical trials (26)

Phase II

Phase II studies, or exploratory therapeutic development studies, have the main purpose of supporting the proof of concept or proof of mechanism that was previously identified in non-clinical stages. They are intended to demonstrate evidence of efficacy and for that reason support the critical "go/no go" decision in what concerns moving forward in the drug development pipeline. Concomitantly, these studies will help defining the target population, exploring the pharmacodynamics relationship between dosing regimen and the effects on disease, determining dosing regimens for future trials and obtaining preliminary estimates of drug effect to be used in the calculation of sample sizes for upcoming phase (5, 24, 27).

Enrolling relatively small number of patients (around 300), Phase II studies are frequently divided into Phase IIa and Phase IIb. This division reflects the change of goals within this phase. While Phase I and Phase IIa are set to provide data on the relationship of dosing and response for the particular intended use, Phase IIb, also designated as late exploratory therapeutics trial, is focused on the clinical efficacy endpoints to be used in phase III. These involve larger sample sizes and tend to last longer (24, 27).

This phase can be particularly distressing, since the inability to define some of the key goals can delay the entire program and ultimately abort the entire study. For that reason, critical decision points and the criteria for the go/no go decision should be clearly determined as a crucial aspect of the Clinical Development Plan (CDP) (24).

Comparison of Clinical Trial Phases				
	Phase I	**Phase II**	**Phase III**	**Phase IV**
Objectives	Determine the metabolic and pharmacological actions and maximal tolerated dose	Evaluate effectiveness, determine short-term side effects and identify common risks for a specific population and disease	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the Food and Drug Administration.
Factors to be identified	Bioavailability Bioequivalence Dose Proportionality Metabolism Pharmacodynamics Pharmacokinetics	Bioavailability Drug-disease interactions Drug-drug interactions Efficacy at various doses Pharmacodynamics Pharmacokinetics Patient Safety	Drug-disease interactions Drug-drug interactions Dosage intervals Risk-benefit information Efficacy and safety for subgroups	Epidemiological data Efficacy and safety within large, diverse populations Pharmacoeconomics
Data Focus	Vital signs Plasma and serum level AEs	Dose response and tolerance AEs Efficacy	Laboratory Data Efficacy AEs	Efficacy Pharmacoeconomics Epidemiology AEs

Design Features	Single, ascending dose tiers Unblinded Uncontrolled	Placebo-controlled comparisons Active-controlled comparisons Well-defined entry criteria	Randomized Controlled 2-3 treatment arms Broader eligibility criteria	Uncontrolled Observational
Duration	Up to 1 month	Several months	Several years	Ongoing (following FDA approval)
Population	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	Individuals with target disease		Individuals with target disease, as well as new age groups, genders, etc.
Sample size	20-80	200-300	Hundreds to thousands	Thousands
Example	Study of a single dose of Drug X in normal subjects	Double-blind study evaluating safety and efficacy of Drug X vs. placebo in patients with hypertension	Study of Drug X vs. standard treatment in hypertension	Study of economic benefit of newly approved Drug X vs. standard treatment for hypertension

Table 1 - Comparison of clinical Trials Phases (adapted from(24))

Phase III

Phase III trials, or therapeutic confirmatory studies, only commence when data generated in earlier phases reveals a satisfactory safety profile and there is sufficient evidence on the experimental drug efficacy (9). Frequently, regulatory authorities require two statistically significant, well controlled clinical trials for the same indication. The main purpose of these trials is demonstrating statistically significant effect on the crucial efficacy measures. Only this way will the approval of the experimental drug by regulatory agencies be possible. Secondary goals for this late phase will likely include evaluation of safety and dosing for package labelling, the use in subpopulations, wider populations and with concomitant medications. Effects on secondary outcomes are also goals at this point. These trials include thousands of patients that represent the intended population to be treated in the market phase. They last for several years and are usually multicentre studies developed worldwide (24).

2.1.3.3. Adaptive Trials

As stated before, clinical trials have the purpose to evaluate the effects of a specific medical or health-related intervention. However, current levels of attrition in clinical trials represent a major problem within the clinical development stage. In order to bridge this translational gap between basic scientific research and new drug successful development there is a need to improve and innovate testing methods so as to ultimately make the manner in which drugs are discovered, developed and brought to final consumers more efficient. In this sense, profound changes in the architecture, design and analysis of clinical trials are occurring in this attempt to bring drugs from “bench to beside” more effectively (28, 29).

One of the tools with potential to respond to this emerging need and contribute to the threatening decline in R&D productivity is the use of Adaptive Clinical Trials. Despite in early stage of development, this approach has been largely recommended and supported both by Food and Drug Administration (FDA) and European Medicines Agency (EMA) (28, 30).

On its Draft Guidance, entitled Adaptive Design Clinical Trials for Drugs and Biological, FDA defines an adaptive design clinical study as “a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analysis of the accumulating study data are performed at prospectively planned time points within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing" (31).

As stated by Mahajan R. and Gupta K, modifications to the trial and/or statistical procedures of the trial after its initiation make clinical trials more flexible, efficient and fast without undermining its validity and integrity (28).

There are several types of adaptive design methods that can be used in clinical trials. They vary from adaptive randomization design, a group sequential design, a sample size re-estimation design, a drop-the-loser design, an adaptive dose finding design, a biomarker-

adaptive design, an adaptive treatment-switching design, a hypothesis-adaptive design, an adaptive seamless phase II/III trial design and a multiple adaptive design (28).

Despite not being the solution to a poorly planned study and unforeseen events, these trials represent an improved tool over the traditional model and ultimately a strong driver for the consistently decreasing number of patients in trials. They have the advantage to improve decision making, allow for a better exploration of dose response relationship, increase patient exposure to the drug doses intended to be developed further, make a better use of resources and costs and allow adjustments when there is the notion that the ongoing trial will likely fail (6).

Some estimates point that streamlining late-stage studies with the use of Adaptive Trials methods would translate into a significant reduction of enrolled participants, namely to about half, and reduce time-to-market by several months. This could represent a saving of hundreds of millions and, most importantly, it could make medicines available earlier. On the other side, some authors argue that this new approach entails some negative aspects, such as hidden costs and the risk of compromising the ability to answer to an experimental question that can be derived from changing the design and conditions of an ongoing clinical trial (30).

It seems clear that adaptive trials need to be explored as a way to maximize clinical trials results. Other than their positive-predictive value, establishing efficacy earlier in the development plan, their negative-predict value is also very important, in the sense that ineffective treatments will be interrupted at earlier stages, avoiding losses in R&D that can be used in other projects (28).

2.1.4. Regulatory Review

Regulatory Review is one of the critical stages in the drug development process. In accordance with Article 2001/83/EC, no medicinal product can be placed on the market of a member state unless a marketing authorization has been granted (14).

2.1.4.1. Marketing Authorization Application

On the European Commission Notice to applicants, Volume 2A - procedures for marketing authorization, it is stated that: “The marketing authorization lays down the terms under which the marketing of a medicinal product is authorized in the European Union (EU). A Marketing Authorizations is composed of: 1) a decision that grants the marketing authorization and that needs to be issued by a relevant authority, and 2) a technical dossier with the data submitted by the applicant in accordance with the articles 8(3) to 11 of directive 2001/83/EC and annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or article 7 of Regulation (EC) No 1394/2007” (32).

The Marketing Authorization Application (MAA) constitutes a body of evidence that is submitted as a dossier and applicants are required to use the Common Technical Document (CTD) format. The CTD incorporates all the necessary efficacy, safety and quality information of a pharmaceutical drug product for which a MAA is intended and is composed of five different modules (14, 33):

Module 1 - Administrative and Prescribing Information

This module is for administrative information and prescribing information, and should contain documents that are specific to each region, such as regional administrative information, a comprehensive table of contents, the summary of products characteristics, the labeling, environmental risk assessment, information regarding market exclusivity for orphan drugs, forms with the experts’ signature and their *Curriculum Vitae* (CV), information relating to pharmacovigilance and to clinical trials conducted outside the EU, and pediatric information.

Module 2 - Summaries

This module contains a general introduction to the drug product, including its pharmacological class, mode of action and intended clinical use. Also, a summary of the quality and a summary/overview of the nonclinical and clinical modules must also be included.

Module 3 - Quality

This section contains the pharmaceutical documentation and general information regarding the drug substance, its manufacturing process, characteristics, validation methods and excipients, among others.

Module 4 - Non-clinical Study Reports

The reports of the non-clinical studies, such as pharmacology or toxicokinetics, conducted for the drug are included here.

Module 5 - Clinical Study Reports

All clinical study reports for clinical trials conducted for the drug go in this module.

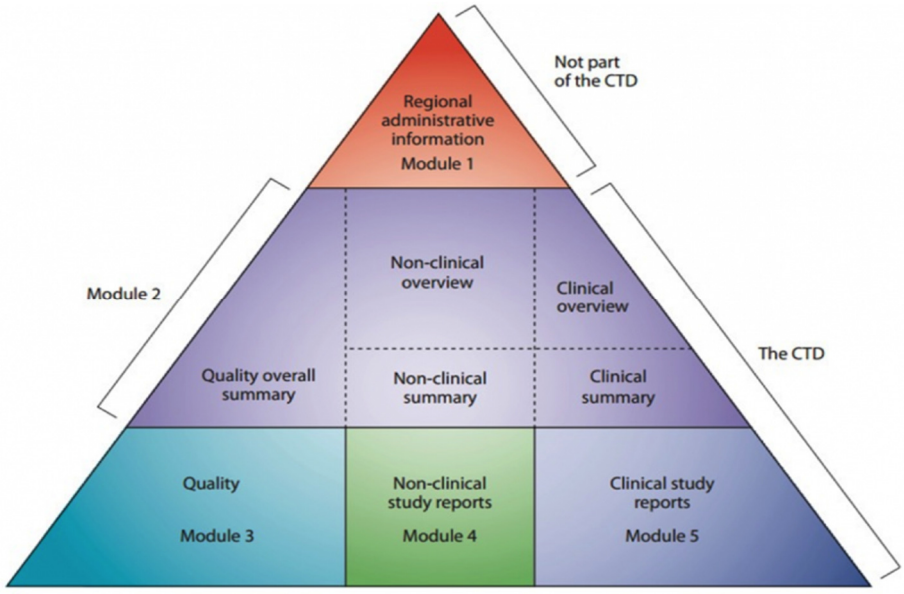

Figure 3 - The Common Technical Document (33)

2.1.5. Post-Approval Research and Monitoring

Research on new medicines does not finish when the discovery and development phases are completed. Because there still remains a lot to understand from new medicine product safety and efficacy long after they are approved for marketing, Phase IV, also known as

post-authorization safety study (PASS), or therapeutic use studies, are required by regulatory authorities (1, 9, 14).

Phase IV studies may be proposed to address several questions. They can result from regulatory authority's requirement for additional long-term surveillance after initial approval of the new drug. This will allow to supplement the data generated on phase III regarding safety and efficacy on the long term. Another reason for these post marketing studies can be part of a defined risk evaluation mitigation strategy. At the same time, Phase IV studies are conducted in order to evaluate safety and efficacy of the treatment on subpopulations, such as elderly, children, and women of childbearing age or patient with comorbid conditions. Drug-Drug interaction studies also are the target for post market studies (14, 24).

2.2. The Pharmaceutical R&D model

2.2.1. A Model at Crisis

One of the main challenges to new drug R&D is the need to balance the demand for innovative medicines with the haste to control health care spending (2). With the biopharmaceutical and biotechnological advances made in the past decades, there were increased expectations that drug companies would be capable of delivering more cost-effective and safer drugs each time faster. However, this was not proven to be as simple and since the beginning of the past decade pharmaceutical and biotechnological industries are facing unprecedented challenges to its current R&D model, showing huge difficulties in translating those advances into successful marked new therapies, despite significant financial investments (6, 34-37).

This phenomenon has been well characterized in literature and some authors have defined it as the "Pharmaceutical Industry R&D Slow Down" (PhIRD-SD). PhIRD-SD is related with the significant decline in new drugs finding by opposition to an increase in R&D costs on an annual basis, and has been extensively referenced in the last years to illustrate the general concern that the current Pharmaceutical R&D model shows no sustainability beyond the current decade (35, 38).

At the same time, we have been witnessing profound shifts in the healthcare marketplace in the past years. It has become notorious that institutions that govern market access have nowadays more influence over the drug approval and reimbursement process. With healthcare budgets becoming increasingly lower, policies on access to medicines are changing and reimbursement models are being strained, resulting in the scrutiny of every new drug (6, 39).

Another relevant and contributing factor to this scenario is the emergence of the generic drugs market that currently represents nearly 70% of all prescriptions in the USA. Despite having a positive direct economic impact in the healthcare systems and payers, improving access to a number of medicines at lower cost, this seems to be shaking industry foundations. Estimates indicate that key patent expirations occurred in the last 5 years will result in losses of hundreds of billions to generic substitution. Without significant increase in R&D productivity, it will not be possible for the pharmaceutical industry to maintain sufficient innovation to replace the loss of revenues due to patent expirations for successful products (34).

The equation becomes even more challenging when it is well-known, and as stated before, that developing a single drug may take almost 15 years and has an estimate cost of more than two billion dollars, achieving success rates of 12% (1, 4).

The truth is that there are many unclear zones that despite an increased investment are very difficult to recognize at the early phases of projects and the main reason for this high attrition rates seems to be the lack of knowledge about the safety, efficacy and quality of the molecule during the first phases of the project. Studies point that in half of lately failed projects, failure is due to lack of efficacy, 30% due to lack of safety and the remaining 20% are not safer nor more effective than the drugs already on the market (34, 35, 37, 40).

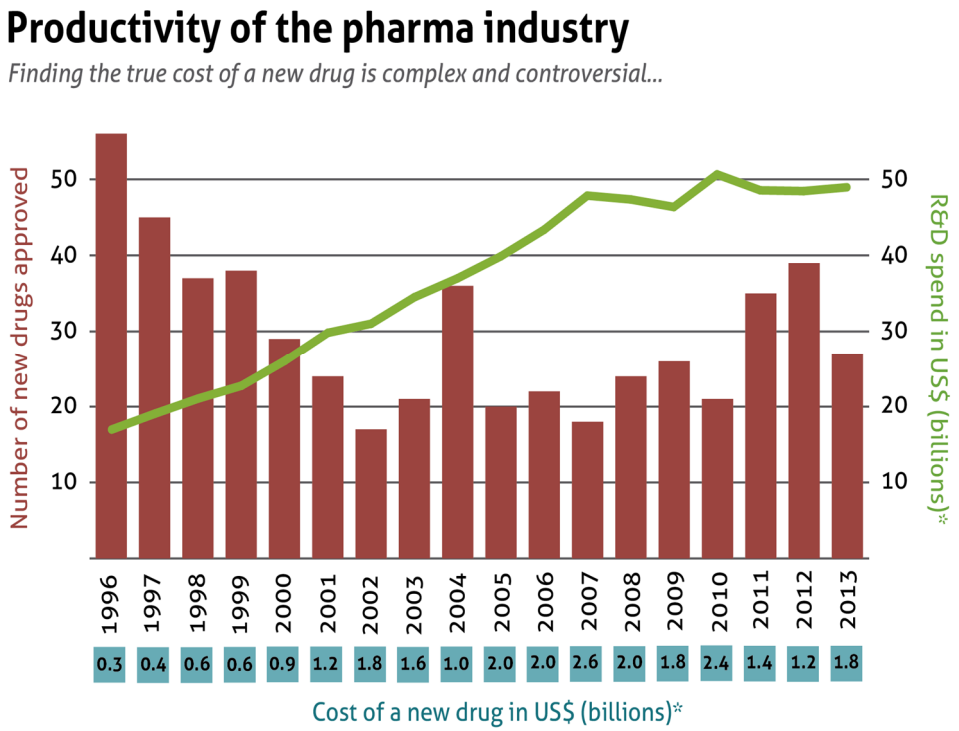

Figure 4 - Productivity of the pharma industry (adapted from (41))

Some root causes to this problem have been identified among the many underlying. They relate to the lack of complete understanding of disease pathophysiology and at the same time with diseases that are each time more challenging. There is also a translational gap reflecting poor translational science that gives way to the high attrition rates. At the same time there are safety issues impacting industry reputation, tougher regulatory hurdles, more complex clinical trials, a regulatory framework that for many years was focused on the bureaucratic side of the process rather than on science, and a clear pseudo-harmonization in an industry that has a true global need. Contributing to this undesirable scenario there were also some risk-taking strategies that included a blockbuster focus in order to align with shareholder expectations, high-risk genomic strategies, attempts to industrialize R&D and the abandonment of integrative pharmacology (35, 37).

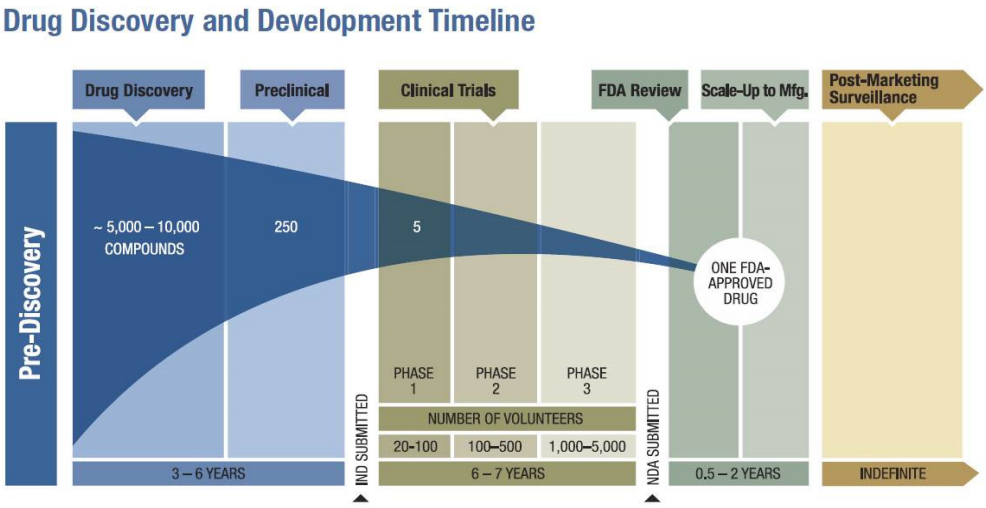

Figure 5 - Drug Discovery and Development Timeline (42)

2.2.2. The Urge for a New R&D Paradigm

Although the pharmaceutical industry has proven to be traditionally resilient, this decline in R&D productivity has had major impact in the pharmaceutical scenario. In order to stop this trend, which has proven to be inefficient and costly, leading to fewer new registrations, a number of worldwide initiatives were created in a new effort to join regulatory entities, industry and academia in the challenging work to identify key bottlenecks in the drug development pathway. Two of the most important initiatives were Critical Path Initiative (CPI) created by FDA and Innovative Medicines Initiative (IMI) developed by EMA (28, 43-45).

CPI is FDA's policy document intended to promote innovation in the scientific processes of drug development. It was set to serve as an integrated strategy for transforming the way FDA regulated products are developed, evaluated, manufactured and used. The critical path opportunity list identifies specific key areas of critical path focus identified by FDA experts and the public. These include (11,14):

- developing better evaluation tools such as biomarkers and new assays;

- streamlining clinical trials by modernizing the clinical trial sciences to make trials each time safer and more efficient;
- harnessing bioinformatics;
- moving manufacturing into the 21st century, using tools such as process analytic technology and nanotechnology;
- developing products to address urgent public health needs including improved antimicrobial testing, new animal models to test bioterrorism countermeasures and vaccine testing;
- focusing on at-risk populations, such as pediatrics.

IMI is Europe`s largest Public Private Initiative and was created to boost the development of new medicines across Europe by implementing new collaborative endeavors between large pharmaceutical companies and other key actors in the health-care ecosystem, i.e., academic institutions, small and medium enterprises, patients and regulatory authorities. IMI's main goal is to unblock barriers to innovation and can be defined by its guideline to (44, 46):

- developing methods and technologies that allow a more precise prediction of safety and efficacy of the new active ingredients;
- means of knowledge and management and;
- promoting advanced and further training.

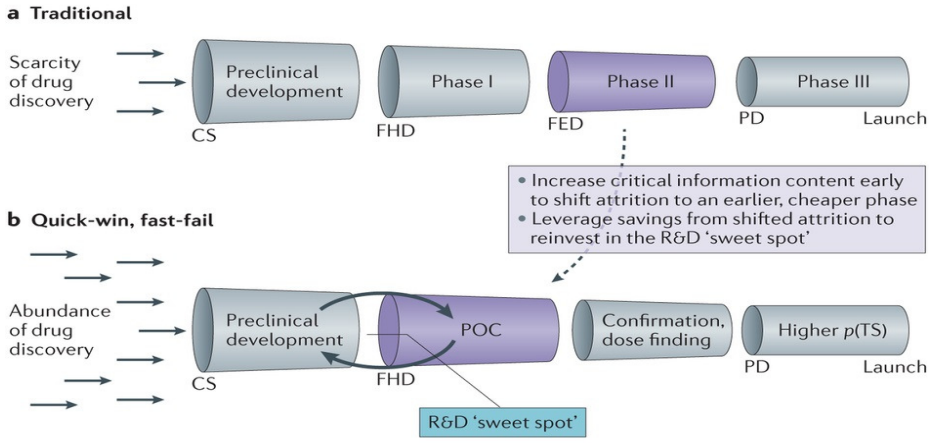

Figure 6 - The Quick-win, fast fail (47)

Other than the outlined initiatives, and in an effort to reverse this slow down trend and boost R&D success, some solutions were identified. As described before, there is a real need to improve the knowledge of disease pathophysiology and overcome the translational gap several. To achieve it, join initiatives supported by regulatory authorities are being developed worldwide, focusing in the collaboration of the several stakeholders and leading to open innovation. In this sense, the support of an innovative environment and improved multidisciplinary-interactions should be enhanced and promoted. Also, it is becoming clear that smaller companies are better tools to promote this innovative environment. A strategy based in building slower for long term success is also important. Clinical trials in sub-populations, the focus on specialized areas and unmet medical needs, where "value" can more easily be demonstrated (orphan products, oncology), and building sets of recognized common standards and policies to address trust and safety issues (34, 35).

In terms of regulatory affairs, some crucial aspects were identified whose implementation can have a beneficial impact in the overall drug development new paradigm, such as a better partnership between regulators, industry and healthcare professionals, an improved regulatory framework aligned with the current science, devoid of the unnecessary administrative burden along with new flexible R&D processes focused in science and "disease need" to be developed in strict collaboration between industry and regulatory agencies. There are other measures that could positively impact the drug development

process, such as the use of “Omnic” research, bioinformatics progress and mass sequencing across both human and animal species/various diseases states and time-point in diseases progression (35, 37, 47).

Another pioneer example is the Accelerating Medicines Partnership (AMP). AMP consists of a collaboration between the National Institute of Health of the USA, 10 biopharmaceutical companies and several non-profit organizations with the goal to transform the current model for developing new diagnosis and treatment by jointly identifying and validating promising biological targets of disease (48).

As we can see, we are now in a critical period where significant changes are taking place, both in the scientific field and in an organizational level. They imply that the various stakeholders should be particularly attentive and able to take advantage of the contingencies to adapt to new market demands and build a R&D development model that is more capable to deliver better, safer and more affordable drugs without these high failure rates. Only thus is it possible that in the next decade we may have a model of scientific development with translational capability where the medical needs of an increasingly demanding population can be met effectively at affordable cost for all the involved stakeholders.

3. Clinical Trials - The Portuguese Reality

A recent report on the clinical trial activity in Portugal published by Apifarma in 2013, indicates that there has been a negative trend in the number of clinical trials applications between 2006 and 2012. In 2006, there were 160 applications and 147 approvals. From 2006 until 2012, we have witnessed a significant slowdown in the number of trials submitted and approved. Data points to a breakdown of 26%, with 2011 being the worst year, with only 87 approved trials out of a total of 88 applications(49). Recent data from National Authority of Medicines and health Products, I.P. (INFARMED), suggests a reversal in this trend, with 2015 having 123 approved trials out of a total of 137 applications (50).

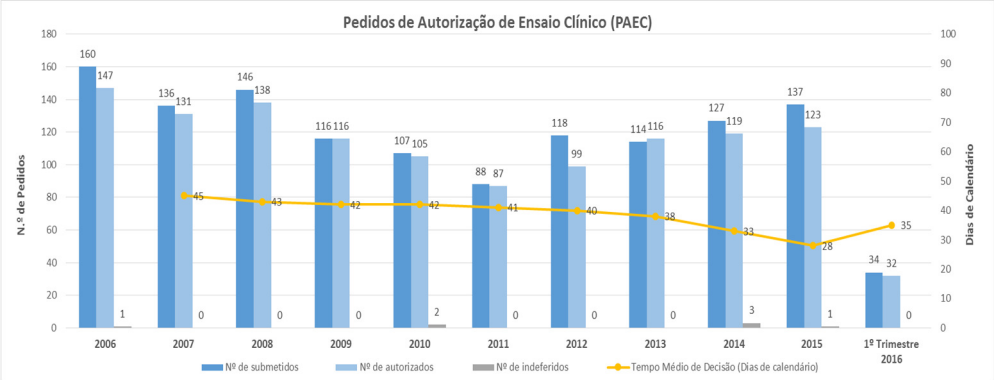

Figure 7 – INFARMED - Clinical Trial Applications 2006-2016 (50)

Looking at the context of the European Union (EU) at the time this report became available, Portugal had a modest performance that translated in a low recruitment capacity. Indeed, the rate of clinical trials per million inhabitants in our country was one of the lowest in Western Europe, showing that we were witnessing to a progressive loss of competitiveness. When analysing the Portuguese case, it was found that the number of sites participating in each clinical trial is clearly low, a situation that contributed largely to the low rates of recruitment. Comparatively, Portugal was just above Bosnia-Herzegovina and Switzerland on this parameter. Another relevant data brought to light with this report was the fact that the investment made by pharmaceutical industry in Portugal was of 36 million euros in 2012. This translated in a public finance saving in medicines and diagnoses procedures of about 3.5 million euros. Also, clinical trial activity was responsible for one

thousand direct jobs in our country. Estimates also indicate that clinical trials in 2012 generated a gross value added of 75 million euros (49).

The reported results are quite disappointing given the fact that, in the words of Nuno Sousa, Vice President of the School of Health Science of University of Minho, "Portugal has critical mass to develop competitive and innovative projects in different areas. We have good universities and research institutes, we have excellent researchers who excel throughout the world and we have examples of business success in the pharmaceutical/health area". In fact, João José Sousa from the Centre of Pharmaceutical Studies of the University of Coimbra stresses that the country "has professionals with technical and scientific preparation that, when added into teams of research and drug development, are very recognized". Indeed, Portugal has a lot of potential in terms of research and development activity and definitely could benefit a lot at several levels if the number of clinical trials increased substantially. As David Braga Malta, founder and director of Cell2B, says “Portugal has its diamond mine in the life sciences”. So, why is this not happening? Why don`t we take advantage of this reality? To better understand why, let us look at the constraints to the full development of this activity in Portugal (51).

Firstly, and in terms of politics and sector strategy, the report identified a lack of acknowledgment of the true strategic value of clinical investigation which coexists with the absence of a real strategy to further develop the sector. This has clearly contributed to the observed loss of competitiveness of our country and to the reduction of international investment. Also, an inefficient system of financial incentives to improve the conditions of clinical trial sites is proactively constraining the activity development. In what concerns legislation and regulatory framework, at the time the report was published, Portugal had very long periods for clinical trials approval when compared with other European countries. Also, requests for clarifications can and do often increase substantially the approval period, contributing to the distortion of the statutory period. Concomitantly, the financial agreement was another handicap, since it had no statutory time of approval which was in the base of a lot of time consumption. As if it wasn’t enough to have the local IRB delayed approval of the financial agreement, the Portuguese Ethics Committee for Clinical Research

(CEIC) approval is conditional until the financial agreement has been approved by the site IRB. The lack of a standardized structure for financial contracts represents an obstacle to the flow of the entire process. Another regulatory obstacle is the fact that, for a clinical trial to start, the National Committee for Data Protection's (CNPD) approval is mandatory. Once there was no statutory approval time, what we had been watching were long and sometimes unpredictable periods of approval. The impossibility of conducting clinical trials in primary care structures was also one of the identified constraints to the activity, along with the lack of a legal framework for the public dissemination of clinical trials and for academic investigation. With regards to infrastructure and organization, the report indicated that there still remains a wide devaluation by the hospital administrations about the strategic potential of clinical trials. These are perceived as cost-generating activities and not as a source of income or savings. There is also the prevalence of a limited and outdated care model at the healthcare services that does not include the research activity in their plans. In the general absence of models of organization tailored to the needs of clinical research, isolated efforts made by some structures were found. At a formative and professional level, authors have identified a severe breach of the financial incentives as well as a reduced impact of research on the valuation of the investigator. The lack of advanced academic and research training associated with the lack of conditions for research initiative of the researcher actively contribute to the divestment of physicians and researchers in clinical research activity. Finally, the lack of a platform to promote and support clinical investigation along with the failure to integrate the different electronic health systems are real technological difficulties very present in our country (49, 51).

In order to end the limitations to the full development of clinical research activity in Portugal, and taking into account that clinical trials offer numerous advantages, such as being a source of economic income that allows significant savings in public health bills and stimulation of the economy, being a source of employment, allowing early access to new drugs, promoting the adoption of best practices in the delivery of healthcare and generating higher quality data for decision support in health, there are some initiatives that need to be implemented (49).

At the governmental level: definition of a government agenda and a strategic plan for the sector, review of financial incentive programs, creation of an independent organization dedicated to clinical research and development of a national strategy for education and dissemination of clinical trial (49).

At a regulatory level: reviewing and streamlining approval processes and authorization of data processing, creation of specific legislation for the disclosure of trials, definition of standard documentation and promotion of academic research process.

At an organizational level: creating management structures dedicated to clinical research, defining a mechanism for the distribution of financial revenues of the studies, creation of conditions for developing trials at the primary health structures and promoting cooperation between different stakeholders (49).

Since this report was published, we have seen some relevant changes in the Portuguese clinical research scenario. In 2014, with new Portuguese law for clinical Investigation, which transposed into Portuguese Law the European directives, a number of changes has been introduced. Through this legislative initiative, the Portuguese Government puts forward a new framework reference for clinical research by creating the National Network of Ethics Committee for Health (RNCES) and the National Register for Clinical Studies (RNEC). At the same time, this new law intends to contribute to the decrease on the evaluation and decision deadlines, streamlining all approval process for clinical trials. INFARMED and CEIC have now a 30 day period to conduct their evaluation (52).

On its document entitled Future Perspectives of Clinical Research in Portugal, the Portuguese Government points out some of their strategic goals (53):

- To increase transparency in scientific activity in submission, opinions, results, used instruments and data;
- Facilitating the creation of research networks;
- Avoid repeated studies;
- Studies publications regardless of the results - publication bias;
- Submission process, assessment and standards to be done in accordance with good, clear and expeditious practices;

- Oversight and ethical regulation during the studies, dissemination and follow-up after the studies;
- Increased resources for regulatory and supervisory processes;
- Monitoring the health research activity in 'real time' – areas, processes, financing, impact;
- Greater accountability of all stakeholders;
- Possibility of studies replication and external validation of the results by access to the tools and data;
- CEIC and Ethics Committees with the capacity to support and promote the quality of research, including through training.

As observed, there is a positive trend in terms of regulatory framework and political vision to enhance clinical research in our country. Despite the numerous problems encountered and the long road we have to travel to reach the desired levels of clinical research and overcome our current refractory position in the European context, it is clear that we have the potential to fully develop clinical trials and that there are several solutions at our disposal.

4. Addressing Unmet Medical Needs

4.1. Rare Diseases and Orphan Drugs

Rare diseases (RD) represent a substantial part of unmet medical needs (54). In the EU, they are defined as disorders affecting not more than 5 per 10.000 persons and they are characterized as being life-threatening or chronically disabling diseases that present high levels of complexity and a low prevalence (55, 56). Although rare, there are now between 5.000 and 8.000 described and identified diseases that affect millions of people worldwide and estimates point for approximately 250 new diseases being described on an annual basis. Lack of knowledge and expertise in RD is a fact and, to date, for the majority of RD the underlying causes remains unknown (55, 57, 58). This poses a real and challenging global health issue. As showed by a recent Eurobarometer study, whose purpose was to assess European awareness on rare diseases, "Europeans have a relatively accurate understanding of what rare diseases are but detailed knowledge and awareness remain low" (57).

While patients with rare diseases needs were devalued and left behind, medicine and research were making significant advances in understanding pathology and developing evidence-based treatments for common diseases. Also, historically, one of the factors that potentiated the lack of investment of the pharmaceutical industry in research and development of new drugs for rare diseases had to do with the limited number of patients who would represent an insufficient return on investment (58).

However, it is obvious now that this trend is changing, as pharmaceutical companies understand the potential revenue involved in R&D and commercialization of drugs to address unmet medical needs, with special emphasis in rare diseases (59).

As stated by Regulation European Commission EC 141/2000 "Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients with more frequently occurring disorders" (60).

To overcome this global problem, the last decades have witnessed an increased stimulation of investment on research, development and marketing of new orphan drugs (57). They

are defined as “medicinal products intended for diagnosis, prevention or treatment of life-threatening or very serious diseases or disorders that are rare” (61).

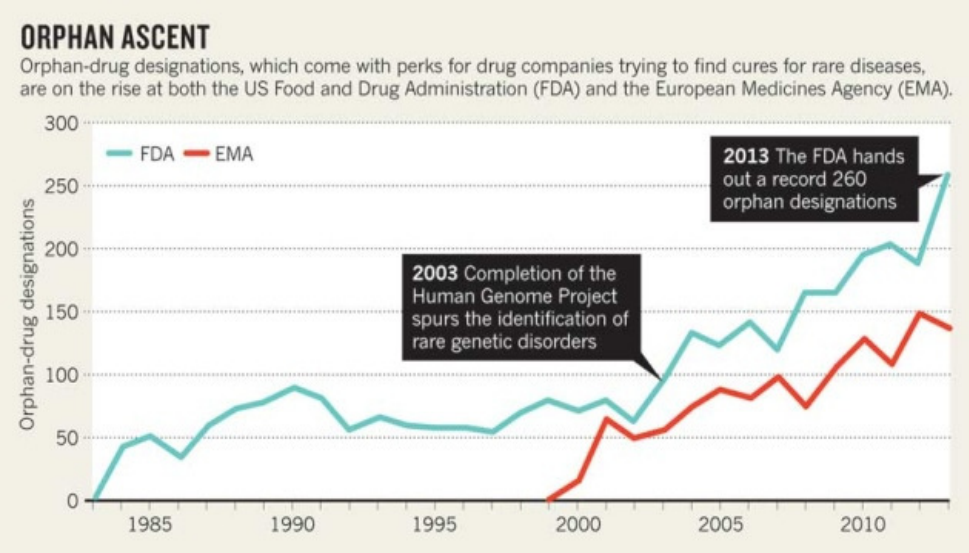

Figure 8 - Orphan Ascent (62)

The first relevant initiative was the US Orphan Drug Act (ODA) in the USA in 1983, a legislation that introduced regulatory and economic incentives to the development of orphan drugs. A recently assessment on the US ODA has proven it to have a tremendous positive impact in the investment of Orphan Drugs in the USA. Around 250 new Orphan Drugs to address more than 200 rare diseases have been approved by FDA in the 25 years following US ODA implementation (58, 63, 64).

In Europe, the adoption of EC Regulation Number 141/2000 of the European Parliament and Council in 2000, the EC Regulation Number 847/2000, together with the implementation of incentives, were essential to stimulate the development of new therapies for rare conditions. In the EU, the responsible entity for reviewing applications for orphan medicinal product designation is the Committee for Orphan Medicinal Products (COMP) of the EMA (58).

Criteria for Orphan Drug Designation
A medicinal product shall be designated as an orphan medicinal product if its sponsor cab establish the following criteria:
That is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects not more than 5 in 10,000 people in the Community when the application is made('prevalence criteria?') or
it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and that without incentives it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary investment ('insufficient return on investment criterion') and, in addition,
That there is no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community ('no satisfactory method criterion') or
If such method exists, that the medicinal product will be of significant benefit to those affected by the condition ('significant benefit criterion?')

Table 2 - Criteria for Orphan Drug Designation (adapted from (58))

If Criteria for Orphan Drug Designation are met, the Marketing Authorization holder has access to some incentives that include: market exclusivity for 10 years, protocol assistance, fee-reduction and EU-funded research (65). For every Orphan Designation Medicinal Product, it is mandatory to use the centralized procedure for marketing authorization and there is the possibility for these products to be approved under exceptional circumstances. Despite this, safety and efficacy of a product need to be established, since regulatory requirements have to be fulfilled the same way as for other medicinal products that do not fit orphan designation (14).

After 10 years of regulation and incentives, there were more than 850 positive opinions that have resulted form 1.235 applications (58).

Figure 9 - European Union Incentives for Orphan Drug Development (66)

Once again, we see that incentives together with a stimulating regulatory environment resulted in a prolific investment in orphan drugs, with initial expectation being surpassed. Patients now have at their disposal medicinal products for conditions that remained untreatable for many years. This has had a profound impact in the quality of life of RD patients, since it resulted in increased health and higher life expectancy (58). However, Orphan Drugs and this new trend in R&D have raised some controversial issues related to pricing. Despite all incentives given, Pharmaceutical companies claim high prices in order to guarantee sufficient return (54). In the opinion of Murphy et al, as new treatments for orphan drugs tend to emerge, the costs associated are likely to get unsustainable both for patients and Public Health systems. This has the potential to derive in a paradoxical effect, that is to have a treatment available but without the possibility to afford it due to its high prices (64).

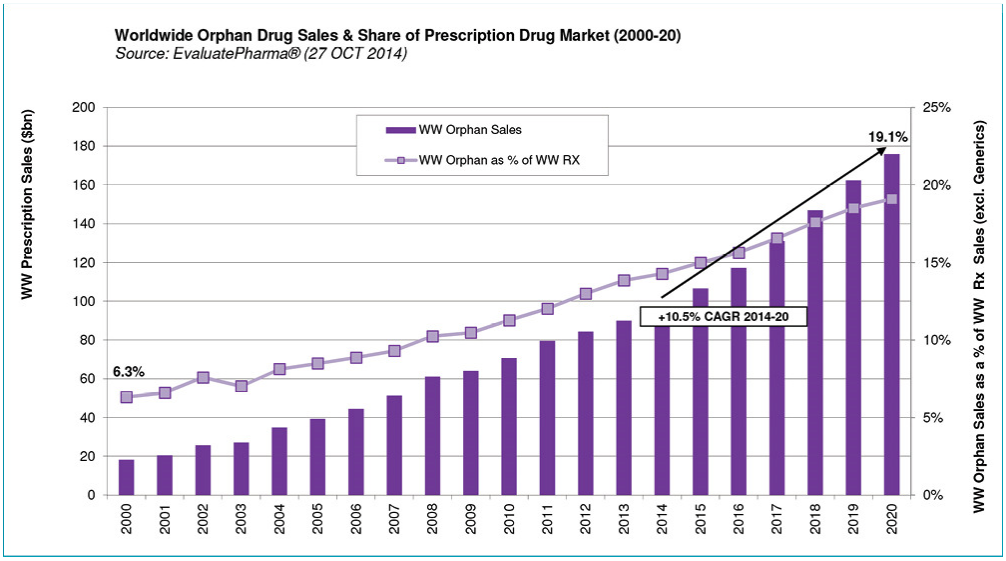

Figure 10 - Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2000-20) (67)

In 2014, EMA launched the adaptive pathway pilot project that consists in an early approval of a medicine intended to treat a restricted patient population supported on small initial clinical studies. As stated by EMA's 2014 annual report "Adaptive pathways is particularly relevant for medicines with the potential to treat serious conditions with an unmet medical need, and may reduce the time to a medicine's approval or its reimbursement for targeted patient groups" (68).

As it is obvious, a global strategic approach, based on cooperation and collaboration of all stakeholders, is required. Only this way will it be possible to prevent significant morbidity and avoid premature mortality, with major impact in the quality of life of the affected patient. At the same time, the emerging cost problem needs to be addressed and a balance between patient needs, health care systems budget and companies R&D revenue return/profit must be found.

4.2. Clinical Trials in Rare Diseases

Conducting clinical trials in RD represents a major challenge. Because the sample size is unavoidably reduced due to the small number of patient having that condition, there is the need to find and adopt innovative approaches in order to minimize the effects of such limitations and optimize the study design and data analysis (69). At the same time, there is frequently scarce information available regarding disease pathophysiology or the natural

history of the disease. Consequently, there's a lot of uncertainty about disease mechanisms, lack of suitable preclinical models of disease and also insufficient insight on potential biomarkers of the disease. Additionally, the inexistence of available therapies for most rare conditions reflects on a significant uncertainty regarding the clinical development program and the most appropriate endpoints to consider for a regulatory approval(70). These facts pose a real challenge to sponsors and regulatory authorities. To address them, there is an effective need to reject the "one size fits all" solution and to start designing trials by using a wider range of strategies (71). As a consequence, in recent years we have witnessed an increase in epidemiology and clinical trials methods that brought a new impulse on the promotion of more effective and efficient research in the field of rare diseases.

Developing and employing innovative designs is one of the approaches, as well as applying specific methodology to observational studies in health outcomes for RD. As we will see, conventional designs are being detracted for designs that tend to minimize the total number of patients or that maximize the number of on-treatment.

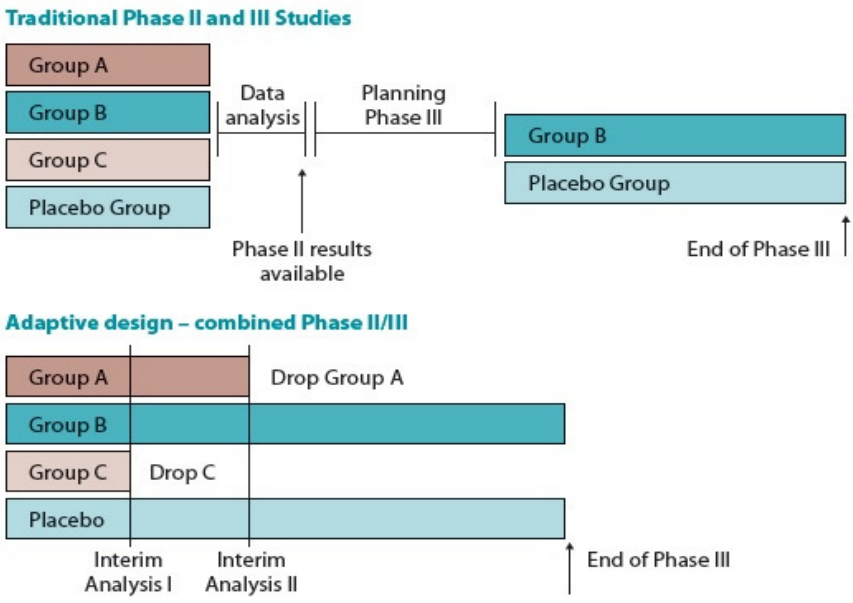

Figure 11 - Adaptive Trials in Orphan Drug Development (72)

Minimizing trial sample size is one of the most common approaches and can be done by (73):

- Designing longer duration trials. This will make reducing the sample size possible by capturing a larger number of events among trial population;
- Focusing on high risk patients. This will allow to reduce sample size and study duration;
- Using genetic testing to reduce variability among participants and allow including patients before symptoms onset;
- Factorial designs, in which several treatment comparisons are carried out simultaneously;
- Using a continuous outcome variable, a surrogate marker, a composite endpoint or repeated measure outcome;
- Developing Clinical Trial Networks for rare diseases;
- Using Adaptive Trials Design, which configures the possibility of modifying some aspect of the trial based on prospectively planned interim data analysis;

A very promising adaptive approach consists on Seamless Phase II/III trials with hypothesis selection at interim. Combining these two stages into one single study can bring significant gains such as reducing the time of decision, planning and implementation of the next phase, saving costs and, above all, obtaining long-term safety data earlier in the drug development process as a result of following up phase II patients (74).

Another type of approach is maximizing on-treatment patients. Studies whose design guarantees patients will be allocated to treatment have the advantage to increase recruitment. As an example, there is the Crossover Design that allows patients to be allocated to the treatment group at one time and to no-treatment group (or comparator) at other time. These studies are particularly suitable for chronic conditions and present stronger statistic efficiency (73).

Observational studies for health outcomes in rare diseases such as patient registries and electronic healthcare databases are of major importance to address the lack of information around rare diseases. These studies are an essential mean to provide major insights in the definition of effective endpoints, identify biomarkers that correlate with clinical endpoints and also allow for a better assessment on the trajectory of the disease progression and variability. However, it seems evident that quite often there is no adequate comparison group against which to compare outcome frequencies in populations with rare conditions. Authors have proposed several methods to analyse health outcomes in observational data. They range from the use of advanced methods to deal with confounding, self-controlled observational study designs, case-control designs to prospective inception cohorts (70, 73)

5. The Clinical Research Coordinator

The CRC is a specialized research professional that is part of an investigational team and works under the direct supervision of a Principal Investigator (PI) (9). The Association of Clinical Research Professionals has defined the CRC role as "A clinical research coordinator, study site research nurse or study coordinator, [who] works at a clinical research site under the immediate direction of a PI, whose research activities are conducted under Good Clinical Practice (GCP) regulation. Among other tasks, CRCs perform site preparation, patient screening and recruitment, patient enrollment, conduct and ensure the quality of case report forms (CRF), maintain source documents and ensure site quality"(75).

CRCs can be of vital importance to the conduct of clinical trials and play a crucial role on the achievement and maintenance of the highest ethical standards, which ensure data integrity, human subject protection, and consequently contribute to the research site's success (76). As stated by Brandt et al, the privileged position at the center of research process provides the CRC with the capability to largely influence the scientific integrity of the research (77). In order to understand this emerging conscience of the CRC importance within clinical research, there is the fact that an increasing number of sponsor companies are avoiding placing trials in sites that do not employ CRC (9). Also, studies have concluded that the involvement of the CRC in a research enhances subject recruitment, retention and general study efficiency (77, 78).

According to literature, a significant number of CRCs have a nursing background (9, 75, 76, 79). However, with the evolving role of the CRC, we now witness to the involvement of individuals from diverse backgrounds. In order to address and manage the diversity of research activities, CRCs are required a wide range of expertise that includes technical, managerial, ethical, regulatory and clinical (9, 75). Although a lot of investment needs to be done in terms of infrastructure for training, career development, continuing education and mentoring of CRCs, there is a positive trend in terms of training that is reflected in the increasing number of formal training courses for CRCs, largely offered by professional organizations, but also some universities offering undergraduate and graduate degrees in clinical research management (9, 77). The value of an CRCs adequate training is increasing

since under-trained CRCs can compromise the research effort, resulting in bad study conduct, low recruitment and retention rates and, more seriously, putting in risk human subject protection (77).

One of the main of aspects of the CRC's function is the requirement to address multiple responsibilities and tasks. CRCs must have very good organizational skills which include the ability to handle multi-tasking (9, 80). According to Kee, there are three soft skills that are mandatory for every CRC: attention to detail, organizational skills and confidence (80).

The role and responsibilities of the CRC will vary depending on the research type, site and country. However, they will most likely include (9, 75, 76, 78, 79):

1- Assisting in the evaluation of new protocols for feasibility at the site, which may include:
   - Reviewing study documents, such as Protocol, Investigator's Brochure (IB);
   - Analyzing subject eligibility requirements and helping determine if those subjects would actually be available;
   - Assessing the site's capacity to meet study timelines in light of site reality and other commitments;
   - Providing assistance in the assessment of site resources to conduct the study (staff, equipment, facilities);
   - Assessing the PI in studying budget analysis and financial feasibility;

2- Preparing the site for conducting the study, which may include:
   - Helping training the study staff;
   - Preparing and organizing study files;
   - Reviewing and/or creating study-specific source documents;
   - Collecting and gathering documents for submission to IRB/IEC;
   - Collecting essential documents needed to initiate study and send them to sponsor;
   - Attending investigator's meeting;

3- Participate in informed consent process, which may include:

- Assisting in the process of writing consents and help sponsor and /or IRB with wording issues;
- Presenting and/or sending the Informed Consent form (ICF) to identified subjects, discussing it with patients and answering to study-specific questions;
- Helping in the process of obtaining ICF signatures and ensuring all necessary signatures and dates were correctly obtained;
- Ensuring all signed ICFs are correctly filed and that all upcoming amendments are implemented and signed.

4- Managing and coordinating the study, which may include:

- Helping PI and Investigators identifying and contacting potential patients to be screened;
- Helping PI and Investigators in the recruitment process;
- Scheduling study visits;
- Assisting PI and Investigators during study visits, ensuring that for each specific study visit all the appropriate study procedures are done according to protocol and IHC-GCP;
- Ensuring correct information gathering source documentation [patient charts and CRF];
- Entering and ensuring all subject data has been appropriately entered into an Electronic Data Capture (EDC) system;
- Reviewing CRF entries and ensuring all AE
- have been entered;
- Collaborating with Clinical Research Associates (CRA) during monitoring visits;
- Responding to data queries;
- Managing study laboratory procedures that may include drawing samples, processing, packing and shipping;
- Managing and reordering study supplies;

- Managing study drug accountability;
- Managing study expenses reimbursements;
- Performing close-out activities;

5- The CRC may be also involved in other duties, such as:

- Collaborating with other hospitals/institution departments, such as Pharmacy, laboratories and study specific departments;
- Ensuring regular communication with sponsors and Contract Research Organizations (CRO), IRB and institution;
- Coordinating and preparing site audits and inspections;

Other than all these activities, CRC is required to be fully aware of the appropriate national and international regulations and also needs to be updated with the most recent industry guidelines (75).

A common problem sites face is the lack of experienced CRCs and also the turnovers. A survey conducted by CenterWatch identified four common reasons that explain this turnover. They include poor compensation, burnout that results from excessive workload, personal life changes and competitive hiring by other sites/companies. At the same time, CRCs often change their position for a higher paying position as a CRA. The loss of a good CRC can and most likely will have a major impact on the ongoing studies and it is crucial that sites recognize the critical role that CRCs play in the study's success (9, 75).

In order to reverse this turnover trend, job satisfaction needs to be nurtured at the research site and opportunities for growth and professional development created. Retaining CRC can be obtained by increasing salary levels, improving benefits packages, flexible hours, hiring of additional staff to assist in study specific activities and creating opportunities for promotions and career advancement (75).

6. Coordinating a Phase 2/3 Clinical Trial in a Rare Disease

Implementing a clinical trial at an investigative site is often a very complex task requiring a strict collaboration between several team members. As we saw above, the CRC plays a very important role in how this task is achieved and at the same time how studies are conducted and how the data is generated.

In this chapter, it will be demonstrated how a clinical trial is implemented in a hospital. The different steps involved in the preparation, conduction and closure of the trial will be described and the fundamental tools and procedures related to a proper coordination of the study outlined. It should be stressed that given the confidential and sensitive nature of much of the information associated with the project, issues that may violate such confidentiality will not be addressed. Therefore, the approach will be focused in a procedural perspective and, wherever possible concrete examples regarding the study will be used.

6.1. The Investigative Site

6.1.1. Centro Hospitalar do Porto – Hospital de Santo António

The investigative site is Hospital de Santo António (HSA), which is part of Centro Hospitalar do Porto (CHP). HSA is dedicated both to patient care and teaching.

In its mission, CHP "aims to excel in all its activities in a comprehensive and integrated approach to safety. It is focused on providing care to improve the health of patients and the population in high differentiation activities and support and coordination with the other health institutions. [CHP] emphasizes and values pre and post graduate education and encourages research in order to contribute to the development of science and health technology"(81).

6.1.2. Departamento de Ensino, Formação e Investigação

CHP has been developing an important role in the promotion of clinical research through its Department of Education, Training and Research (DEFI) whose main intervention areas consist on the training of professionals of the CHP and also the encouragement and support

for scientific research in healthcare. This department is responsible for the coordination of the clinical trials conducted at CHP and the management of research resources. In 2014, and according to this department's annual report, there were 81 trials, including ongoing or trials that were closed that year at CHP (81, 82).

6.1.3. Unidade Corino de Andrade

This project is being conducted at Unidade Corino de Andrade (UCA), previously designated as Unidade Clínica de Paramiloidose (UCP). UCA is an Ambulatory Care Unit that gathers several medical specialties such as Neurology, Cardiology, Nephrology, Dermatology, Physiatry, Psychiatry/Psychology and also Nursing support. It is part of HSA and is included in the Department of Nervous System Diseases and Sensory Organs. Since 2006, UCA has been playing a proactive role in conducting clinical trials and other disease related research studies, and is now one of the CHP unities that have given greater contribution to clinical research at this hospital. In 2015, it became a Portuguese reference center for Familial Amyloid Polyneuropathy (FAP).

6.2. The Target Disease: Familial Amyloid Polyneuropathy

FAP is a hereditary systemic amyloidosis, with an autosomal dominant transmission, with adult onset, progressive, disabling and fatal (83, 84). It is a rare disease whose main locus is in Portugal. Estimates indicate that about 1.500 patients currently exist in our country and 10.000 worldwide (84, 85). The first symptoms of the disease usually occur in adult life, around the age of 30. The disease manifests itself through a sensory, motor and autonomic neuropathy, leading to progressive disability with a fatal outcome after eleven-year progression, on average (84). It is caused by a Transthyretin (TTR) gene mutation (the most common in Portugal is VAL30MET), a protein which is mainly produced in the liver. The functional form is a tetramer that becomes unstable in the presence of the mutation, leading to the breakdown in subunits and consequent formation of amyloid substance (86, 87). Current available disease therapies in our country consist of liver transplantation, which was the only available treatment for many years, and a TTR stabilizer (tafamidis) that was the first drug approved for this condition in Europe in 2012. Currently representing a very important investment in the future of FAP patient treatment, and with the focus on

TTR gene silencing technology, there are two ongoing multicenter phase III clinical trials using SiRNA and antisense oligonucleotides. Both are strategies to “knockdown” the expression of TTR protein on liver by leading to the destruction of the corresponding mRNA (88, 89).

Figure 12 - Distribution of FAP around the World (85)

6.3. The Investigational Medicinal Product: ISISTTR-Rx

ISISTTR-Rx was developed by IONIS Pharmaceutical and is a new, first-in-class drug. It was created with the main purpose of reducing the supply of TTR protein in patients with TTR amyloidosis. This antisense oligonucleotide is being studied in a clinical trial and was conceived to directly target and reduce TTR at a genetic level inside liver cells. It is expected that with the decrease of TTR supply disease progression slows down or even stops (85). Because this IMP addresses a rare, life-threatening, severe disease affecting no more than 5 in 10.000 patients in the EU, ISISTTR-Rx has been granted the Orphan drug designation from EMA in early 2014 (90).

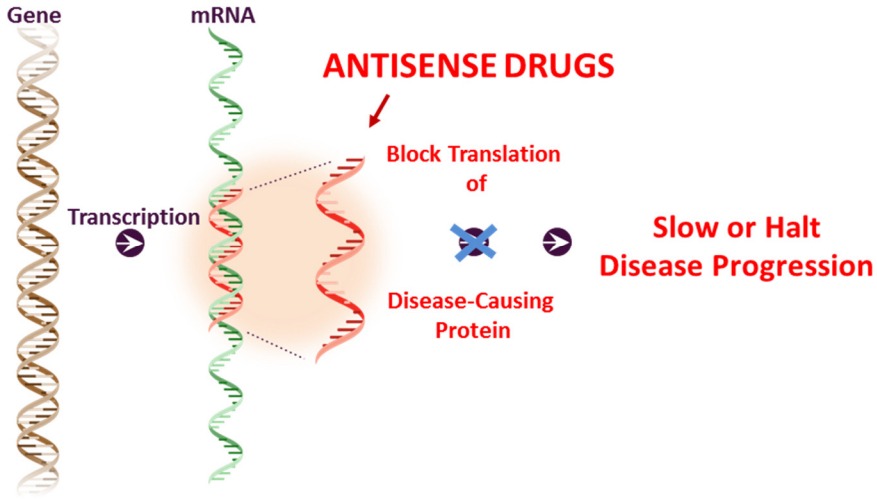

Figure 13 - Antisense Drugs (85)

6.4. The Clinical Trial

ISIS420915-CS2 is a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with FAP. Since 2015, an Open-Label extension of ISIS420915-CS2 called ISIS420915-CS3: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with FAP is also ongoing.

6.5. Essential Tools to Coordinate Clinical Research

6.5.1. Good Clinical Practices

ICH-GCP E6 (R1) defines GCP as “an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical trial data are credible” (91, 92).The fundamental principle of GCP is that, in research conducted in human beings, the considerations related to the well-being of the study participants should never be preceded by science or society interests (93).

The principles of GCP can be found in the GCP Directive 2005/28/EC, the Clinical Trials Directive 2001/20/EC, and in ICH guideline on GCP-ICH Topic 6. ICH E6 covers essential definitions, ethical committee review, the role of investigator and sponsor, the expected contents of the clinical trial protocol and IB. ICH-CCP E6 is intended to provide a unified standard for the EU, USA and Japan, by streamlining the mutual acceptance of clinical data by regulatory authorities (14).

The main ICH-GCP principles are:

- Clinical Trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki;
- A trial should only be initiated and continued if the anticipated benefits justify the risks;
- The rights, safety and well-being of trial subjects are the most important considerations, and should prevail over interests of science and society;
- The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial;
- Clinical trials should be scientifically sound and be clearly described in a detailed protocol;
- A trial should be conducted in compliance with the protocol that has received prior IRB/IEC approval;
- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician;
- Individuals involved in conducting a trial should be qualified by education, training and experience to perform his or her respective tasks;
- Freely-given informed consent should be obtained from every subject prior to clinical trial participation;
- All clinical trial information should be recorded, handled, and stored in accordance with applicable good manufacturing practice (GMP) and used in accordance with the approved protocol;

- Systems with procedures that assure the quality of every aspect of the trial should be implemented (14, 92).

CRC's should have training in GCP completed before starting study related activities. Updated GCP training documentation from all team members must be filed in the Investigator Site File (ISF).

6.5.2. Regulations and Guidelines

Drug development is highly regulated. Every CRC should read and possess a good working knowledge of the regulations and guidelines associated with clinical research.

In Portugal, the conduct of clinical trials on medicinal products for human use is regulated by Law Nr. 21/2014 of 16 April (Clinical Research Act) that transposes Directive 2001/20 / EC of the European Parliament and of the Council of 4 April (94).

As stated in EMA's webpage: "Regardless of where they are conducted, all clinical trials included in applications for marketing authorization for human medicines in the European Economic Area (EEA) must have been carried out in accordance with requirements set out in Annex 1 of Directive 2001/83/EC". This means that:

- Clinical trials conducted in the EEA have to comply with the EU clinical trial legislation (Directive 2001/20/EC);
- Clinical trials conducted outside the EEA have to comply with ethical principles equivalent to those set out in the EEA, including adhesion to International GCP and The Declaration of Helsinki (95).

Recently, regulation Nr. 536/2014 of 16 April 2014 was adopted by the European Parliament and the European Council concerning clinical trials on medicinal products for human use, and repealing Directive 2001/20 / EC. This legislation will be directly applicable to the legal framework of the Member States six months after publication, but not before May 28, 2016 (94).

The main Guideline for Clinical Trials In Europe is Eudralex's Volume 10: Clinical Trials Guidelines. This Guideline is divided in 6 chapters that cover: Application and Application

Form; Safety Reporting; Quality of the Investigational Medicinal Product; Inspections; Additional Information and Legislation (96).

6.6. The Stages of a Clinical Trial at the Investigative Site

At the investigative site, a trial undergoes three separate stages: Trial Preparation, Conduction and Closure.

6.6.1. Trial Preparation

There are many activities that take place prior a site is selected to participate in a clinical trial and a number of steps that must be completed before a selected site can start enrolling patients. From site evaluation/selection, assessment of protocol feasibility, budgeting, site preparation, application of trial to competent authorities, investigator meetings, to site initiation visit (SIV), CRCs are closely involved in all these activities and are required to have a thorough understanding of each of them.

6.6.1.1. Site Evaluation and Selection

Site evaluation and selection are usually the first contacts between sponsor and site and it represents the moment when it is decided if a site will be selected to participate in the trial. Usually, the first contact is made by telephone. If there is a corresponding level of interest, a visit will most likely be scheduled. While for the site this visit will determine whether it will be selected to participate in the trial, for sponsors it consists of a useful tool to select the best sites to be a part of the clinical trial. Many companies require a signed confidentially agreement prior to making available study documentation, such as the protocol. Some sponsors and CROs send preliminary questionnaires to the site in order to assess its suitability for a given study. At these visits/contacts, the sponsor's main interest is to evaluate the investigator's experience, expertise and motivation to be part of the study. They will also focus and assess if the site has potential patient population available, adequate staff and facilities. Usually, a positive indicator will be the previous participation on similar trials (9).

During this assessment period, it is also essential that the site carefully analyses the protocol and all study requirements essential to the conduct of the trial. A detailed read of the protocol or any another study related materials made available is highly suggested, both by Investigators and CRC, in order to decide if their participation is realistic and, if so, in what terms.

A site should always try to answer the following questions:

- What do we know from previous experiences with this sponsor?
- Are the timelines and the proposed number of patients to be enrolled realistic?
- Are the eligibility criteria realistic for the patient population in cause?
- Are there particular exams that require specific equipment to be ordered?
- Will our patients benefit from this study?
- Are we capable to be compliant with the protocol?
- Are patient expenses covered?
- Is the budget clear and reasonable?(9, 75)

As stated before, the presence of a CRC from early stages of trial is fundamental. It will reveal that the site has adequate staff, which is regarded as a good predictor of trial success at that site. Besides, many sponsor companies avoid sites that don't employ CRC (9).

6.6.1.2. Preparing Trial for Application

When the site is finally selected, there are a number of documents that need to be gathered so that the sponsor or CRO can prepare the trial for application. In Portugal, the application of a clinical trial for a new IMP comprises the application for authorization to the National Competent Authority - INFARMED and the application to CEIC. Additionally, the application to the CNPD is also required in order to ensure the confidentiality and security of personal data that will be collected during the trial. Only after authorization of these three institutions the sponsor may initiate the clinical trial (52).

The CRC will be responsible, with the help of the CRA or Study Start-up Associate, for collecting the documentation to set up all the submission packages. Among others, they

will likely include: signed protocol signature page; PIs CV; written declaration by the director of the health unit/institution that it is constituted as the trial site, with a brief description of the site's conditions, signed financial agreement and the study coordinator's declaration. This stage can be particularly confusing since there's a lot of documentation. A checklist may be appropriate at this point.

6.6.1.3. Financial Agreement

Protocols are becoming very complex and they request more and more specific procedures every time. This represents a challenge for sites because they need to be assured they will not be losing money with the trial. The hidden costs are many and sites need to be very careful when negotiating and approving financial contracts. Most sponsor companies will propose a system that operates on a fee-for-service basis, assuring this way that they will only pay for actual work performed, and others choose to determine a range or a single per-participant amount that they will pay and nothing more. No matter the approach, this is a crucial aspect in trial preparation and the CRC can have an important role by helping the PI to analyze the complexity of the protocol and its translation into the financial agreement. Also, experienced investigators and CRC know that some particular issues need to be taken into account, i.e., travel expense fees and a non-refundable upfront amount to help start up the trial. One of the problems that usually arise from this process is that each institution has its own template and rules and for that reason the time to prepare, review and approve the financial agreement tends to be very long, sometimes contributing for the delay of the trial initiation. With the new law and the new statutory timelines for financial agreement review and approval, it is expected that this ceases to be a problem (9, 49, 53).

6.6.1.4. Investigators Meeting

Despite not being required by regulation, this meeting is often the first time that Investigators and team staff meet the sponsor representatives. They are usually arranged for multi-centers trials and constitute an excellent opportunity for training and to clear many of the doubts resulting from the initial protocol reading. The CRC should always participate in these events and carefully take notes and get acquainted with all the sponsor and CRO representatives (9, 75).

6.6.1.5. Site Initiation Visit

SIV, also known as start-up visit, will be performed at the investigative site before the study starts and usually after all approvals are granted. This visit, normally conducted by the CRA, is a good chance for all team members who were not present at the investigator meeting to become familiar with the study. The content of this initiation meeting should cover aspects such as a detailed overview of the protocol, drug accountability, AE reporting, CRF, Investigator Responsibilities and other study specific matters (9, 75). The CRC will be responsible for arranging the meeting at the site and usually assuring the entire team is present. This meeting works as training for the team members and should be recorded on a specific log and filed on ISF.

6.6.1.6. Study Organization

After the SIV, and if all authorizations have been granted, the site is ready to start recruiting patients. For the CRC, this is a crucial time for planning and setting things for the study to commence. Below is a list of some of the crucial aspects that need to be arranged beforehand and that frequently have already been defined previously:

- Define who will be responsible for screening, consenting and randomizing patients;
- Identify and define where study procedures will be conducted at the site, namely appointments, exams, blood draws;
- Identify who will take responsibility for any samples, EKGs and other protocol related exams;
- Define who will complete CRFs and study documentation, and who will be responsible for reporting Serious Adverse Events (SAE).
- Ensure all staff is in place and has been appropriately trained before doing any study-related procedure;
- Ensure the responsible pharmacist has the IP ready or any other protocol required medication available;

- Ensure all study material and supplies necessary to the conduct of study are available at the site and properly stored;
- Ensure there is storage for all study files and materials;
- Ensure availability of all the basic documents, such as updated and translated ICF, questionnaires and patient related materials;
- Ensure that the team members involved in those activities were given specific training and access to online study platforms, such as Interactive Voice/Web Response Systems (IVRS/IWRS) and EDC.

6.6.2. Trial Conduct

This stage of trial formally begins when the first patient is recruited to the study. During the trial, there are a number of things that a CRC needs to have in mind and use. We will now focus on the main documents, procedures and aspects that are involved in this stage of the trial.

6.6.2.1. The Protocol

The protocol is a basic tool for clinical trials. It can be defined as a plan for the study and it is intended to describe its objectives, design, methodology, statistical considerations and the organization (5, 9). A well-written and sound design protocol will allow the study to generate valid data (9). Also, they are an essential part of the CDP since they specify the conditions that will allow and lead to significant and vital results in clinical programs (5).

Well-designed protocols should include the following elements: Background and rational; Study objectives; Experimental design and methods; Schedule of assessments; Subject selection criteria; Trial Procedures; AE Reporting; Trial medication; Premature withdrawal; Subject replacement policy; Criteria for excluding data; Data analysis/statistical methods; Quality Control Assurance; Data handling and record keeping; Ethics; definition of end of trial, Sponsor discontinuation criteria and Signatures. As stated by Edwards LD *et al*. "…to prepare appropriate protocols, staff must understand research design and statistical inference for clinical research, state-of-the-art research designs and trials, therapeutic area

guidelines, good clinical practice, regulatory requirements, guidelines and country-specific issues, national and international medical practices, sponsor protocol reviews and approval procedures, and possess in-depth investigational product-disease knowledge" (5).

Over the past years, protocols have become increasingly complex and more demanding in their requirements. This is reflected in the rising number of procedures per protocol and a significant increase in the total number of eligibility criteria. This places a major burden on study sites with negative impact on research. CRCs are required to have in-depth knowledge of the protocol they were assigned to implement in order to avoid protocol deviations that compromise data integrity and the participants' safety (9).

One of the aspects that make protocol implementation even more difficult and complex is protocol amendments. These formal changes to protocol are very usual in research and tend to have a negative impact in the initially planned timelines. A recent analysis conducted by Tufts CSDD indicates that at least one substantial protocol amendment is implemented in about 60% of all clinical trials. Other than timelines delays, these involve major costs with significant impact in study budget. It was found that a phase III amendment alone can cost around half a million dollars to implement and delay the study three months on average when compared with studies without amendments. Other important conclusions from this analysis indicates that amendments are more frequent on phase II studies and that protocols with amendments screen and enroll less patients than the original plan when compared with protocols without amendments. One must also bear in mind that nearly 40% of amendments are due to safety issues and 20% due to efficacy (97).

CRC need to be prepared to handle protocol amendments. Indeed, they can represent an extra burden on daily activities, with the need to update several study documents and procedures. Also, for some of these amendments the need for re-consenting may be necessary and in some cases the financial contract needs to be reviewed and amended.

6.6.2.2. The Informed Consent

The ICH-GCP defines Informed Consent as "A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated ICF" (92). It is essential that Investigators and CRCs understand the significance of obtaining valid and adequate informed consent from trial participants as a determining element for the protection of the rights and welfare of human subjects (98). "Voluntarily" and "Informed" are the cornerstone of ethical conduct in clinical research.

A properly conducted informed consent process is compliant with the notion that any subject fully understands what is being told and is free to say "No" and that his or her decision won't have any repercussion (9). As referred by the Council for international Organizations for Medical Sciences (CIOMS) "Informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information (…) in language that suits the individual's level of understanding (…) the investigator must ensure that the prospective subject has adequately understood the information" (98).

It is fundamental to consider the following elements that are inherent to the process of informed consent:

Environment: In order to facilitate a constructive interaction and dialogue between subject and the person involved in obtaining consent, the potential participant should be given an adequate period of time on a private, confidential and safe setting, such as a physician's office or an examination room (92, 98).

Assessment of the capacity to consent: It is fundamental that all subjects have the cognitive ability to give legally effective informed consent. If this is not possible, consent must be obtained through their legally authorized representative (92, 98).

Presentation of the elements of the informed consent: The essential and required elements of the informed consent are to be presented and discussed, ideally in a structured manner, in order to facilitate a dialogue with reinforcement and elaboration of the relevant information. It is advisable to ask open-ended questions with the purpose to identify and minimize potential points of confusion. This will help avoiding "therapeutic misconception" that is related with the subject overestimation of the direct therapeutic benefits and/or underestimation of risks regarding participation in the research (92, 98).

Use of a delayed consent procedure: Time to decide is very relevant in this process. Despite it may vary, depending on the research complexity, it is advisable that subjects are given the necessary amount of time to consider every aspect of their involvement. This will help to reduce the coercion or undue influence. It is advisable that subjects have the possibility to take ICF home for further discussion and analysis with their relatives (9, 92, 98).

Assessment of the subject's comprehension: People involved in the Informed consent process have the legal and ethical obligation to guarantee the subject has enough knowledge and comprehension of all the elements of the informed consent that enables them to grant an informed and enlightened decision. One way to ensure this is to ask the subject to give an explanation on the research presented in their own words (9, 98).

Documentation of the Informed Consent: Documentation of this process is a crucial aspect. The person responsible, that can be the one who signs, must be qualified to prove that the subject has given legally effective informed consent. Usually, and for studies involving investigational drugs, the PI or the sub-investigators should be involved in the process and documentation of the informed consent. In certain cases, such as clinical trials for some FDA approved drugs or procedures involving minimal risk, it is possible for non-physicians to conduct and document this process. It is requested that both the person responsible for documentation and patient sign and date the ICF, preferably in each other's presence (9, 92, 98).

Ongoing Consent: Because research is an ongoing process with new data and information becoming available quite often, participants have to be informed and re-consent as part of compliance with regulatory requirements and ethical conduct (92, 98).

6.6.2.3. Subjects Recruitment and Retention

Subject recruitment and retention represent crucial factors for the successful conduction and completion of clinical trials (75). It is known that a large percentage (about two-thirds) of clinical trials effectively fail to enroll the initially determined number of subjects (9, 99). This has a significant negative impact on research and contributes to higher development costs, increase in medicines cost that by its turn becomes available later to patients. This overestimation of the number of potential candidates frequently results from the fact that investigators only look for patients who match the overall diagnosis. Indeed, this assessment has to take into account several factors, such as the protocol, target population, human and physical resources, recruitment period, the existence of competitive studies, incentives, etc (9). Protocol assessment, and more specifically exclusion and inclusion criteria analysis, is an essential step for developing a realistic estimate. CRCs are a major asset in helping PI to perform an accurate estimate. As stated by Nahler G., “In order to be realistic, the number of cases promised in any clinical trial must be divided by a factor of at least ten” (100).

Although recruitment is a very important aspect for clinical trials, once patients enroll in the trial, it is also determining that they stay until the study it is completed. Because high levels of dropout and discontinuation rates are a very real threat to clinical trials success, they have to be anticipated and incorporated in sample-size projections, in order to determine the necessary number of patients that are to be recruited (75).

There are several causes for patient discontinuation. They can be related with medical reasons (lack of efficacy of the drug, intolerable AEs, SAEs, patient health deterioration, etc.); patient compliance and cooperation reasons (recurrent incompliance with protocol, lack of cooperation with study staff in study procedures, etc.); trial-related reasons (safety

concerns, business reasons, benefit proven to be so good that it is no longer ethical to continue trial and keep other patients without access to treatment, etc.) (9).

In order to avoid and minimize dropouts, there are a number of simple things that can be implemented in research's daily practice that will help patients feel better and reduce the burden associated with trial procedures. They include

- Avoiding long periods of waiting in study visits.
- Treating patients with respect and empathy.
- Having the same people dealing with patient and avoiding substitutes.
- Asking patients how he or she is feeling.
- Allowing patient to ask questions and express their concerns.
- Using Home Care Services, when possible, to reduce travel burden.
- Timely reimbursement for travel or any other study-related expenses.

CRCs are often responsible for helping PI assessing the protocol and to determine a realistic number of patients to recruit. This was indeed a challenging task, since in this case the number of patients to include depended on the number of non-responder patients to the current available therapy, which was very difficult to predict.

As we can see, timely and appropriate enrollment and retention are top priorities during the development of clinical trials. As Ken Getz, associate professor and director of sponsored research at Tufts CSDD, states "The need to improve patient enrollment and retention rates is urgent and becoming more so, especially as we enter the era of stratified and precision medicines, in which investigative site needs to recruit volunteers from more narrowly defined, and therefore more limited, sub-populations" (101).

6.6.2.4. Case Report Forms and Electronic Data Capture

CRF is defined as "A printed, optical or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject" (102). CRFs have the purpose to standardize data collection and are also crucial to ensure that

medical, regulatory, statistical and data management needs are met (9). A well-designed CRF is of major relevance, since it will help assessing both safety and efficacy of the investigational drug properly and accurately (102). There are two types of CRFs, paper and electronic. Paper CRF is a traditional way to capture data, however, the use of EDC systems in clinical trials as become a generalized practice. Working with CRF represents one of the most time-consuming and significant tasks of a CRC's daily practice and is also one of the most crucial aspects impacting the conduct and results in clinical trials. Every time a patient performs a visit, the SC or responsible person for data entering needs to record that data in the CRF or EDC. It is crucial that data is recorded in an accurate, complete and legible manner (9).

The CRC is commonly the main responsible team member for entering all study-generated data in the EDC, with the support of Investigators. Usually, and before any data is entered, there is specific training for this task. Timely and accurate data entry is very important. Most sponsors have specific timelines and expectations for site staff to enter date in the EDC and for query resolution (9).

6.6.2.5. Adverse Events and Safety Reporting

Safety reporting during the conduct of a clinical trial represents one of the most important tasks for investigators and CRCs. It is also one of the areas where more difficulty is present since there seems to be some misunderstanding about what and how it needs to be reported. This appears to result from the differences between clinical practice compared to research practice and also, in some extent, to the lack of information concerning adequate and actual safety reporting. It can be challenging and confusing both for Investigators and CRCs to understand that in clinical research the definitions used for AE reporting respond to regulatory rather than to clinical definitions (9).

The purpose of collecting AE in clinical trials relates with the need to detect and characterize Adverse Drug Reactions (ADRs), investigate the relationship between dose and safety, protect trial subjects from harm and respond to legal obligations (14).

Portuguese law 21/2014 for clinical Investigation describes (52):

- "AE as any unfavorable clinical event, regardless of the existence of a causal relationship to the intervention;
- SAE or serious adverse reaction (SAR) as any event or adverse reaction that results in death or danger of the participant's life, requiring hospitalization or prolongation of hospitalization, in disability or in significant or lasting disability, in fetal distress, fetal death, in anomaly or birth defect, or which is considered clinically relevant by the investigator".

It is very relevant to clearly distinguish between the terms "serious" and "severe". The first relates with the definition above and is used to categorize events (i.e., if they meet the definition of serious or don't) while the second is used to describe the intensity of the event without regard to whether or not it meets the criteria for being classified as serious. For example, a patient can have a severe toothache, but that may not be considered a serious event (9).

Article 16 of Clinical Trials Directive 2001/200/EC describes the requirements for notification of AEs (14, 17):

- "The investigator shall report all SAE immediately to the sponsor, except for those that the protocol or IB identifies as not requiring immediate reporting and the immediate report should be followed up by detailed written reports, identifying subjects by unique codes.
- AEs identified in the protocol as critical to safety evaluation shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol".

Investigators need to collect, assess and report all AEs that happen during the clinical trial. It is very important to gather detailed and accurate information related with the event and document it in the medical chart or other appropriate source. It should include the event term/description, onset date and time, duration, severity, relationship to the study drug and whether it meets serious criteria or not. All the AE are required to be recorded in the

CRF. In case the AE is considered serious, investigators are expected to report it to sponsor with urgency, usually within 24h after becoming aware of the event (9).

One of the most important CRC tasks is to help Investigators to notify the sponsor of all SAE occurred with patients participating in the trial. It is very important that coordinators and Investigators work closely, in order to have the event information submitted within the required timelines and to closely follow-up with patients.

6.6.2.6. Audits and Inspections

Audits and Inspections are carried out by sponsors and regulatory authorities and have the purpose to implement quality assurance and also to evaluate quality control processes at investigative sites (75, 103). ICH-GCP defines audits as “a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s)” (104).

Audits are commonly conducted by sponsors. This right is based not only in regulations but also in the contractual aspects between sponsor and Investigator, which frequently foresees them (9).

There are two types of audits. The first are called routine audits and have the main purpose to ensure site compliance with GCP, regulations and protocol. Routine audits frequently result from sponsor suspicion that a particular site is to be inspected by a regulatory authority, such as FDA or EMA. Sites that have high rates of enrollment, have several studies that contributed to the MAA or that had a significant number of patients in a primary registration study are the most likely to be selected for audits. Whenever there’s suspicion or evidence of incompliance, sponsors conduct for-cause audits (9, 103).

ICH-GCP defines Inspections as “The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of

the trial, at sponsor's and/or CROs facilities, or at other establishments deemed appropriate by regulatory authority(ies)" (104).

According to EMA Procedure for coordinating GCP inspections requested by Committee for Medicinal Products for Human Use (CMPH), "any clinical trial included in the application could be subject to the Inspection" (105) Its main objectives are:

- "Determine whether the trial was conducted in accordance with applicable regulatory requirements, which include local regulation and ethical standards, and the CPMP/ICH/135/95 Note for Guidance on GCP, and Directive 2001/83/EC;
- Provide answers to questions arising from the assessment process where it has been determined that these can best provide through inspection;
- Determine whether the data submitted in the dossier are credible and accurate"(105).

The same way as audits, inspections can be Routine or For-cause, depending on the trigger reason and are frequently requested at the time of MAA initial review. They can go from a simple verification of the GCP compliance statement, to the examination of concerns with the IMP or any serious and/or persistent GCP non-compliance previously reported (105, 106).

One of the most stressful and demanding aspects of clinical trial coordination is the site preparation for an audit or inspection. Despite the fact that the best way to prepare is to comply and perform correctly on a daily basis, there are always a number of things that need a careful review before an audit/inspection takes place.

Usually, sites are notified in advance. Depending on the type of inspection/audit, this period can vary from a few days to a few weeks. In case of serious concerns, inspectors can appear at site without notification. It is important that both PI and CRC are present and available throughout the inspection. A collaborative approach is preferred than antagonism and material/documentation should be available at request. It is important that

Inspectors/auditors don't have free access to the files and the site team should only answer to what they were asked and no extra volunteer information should be given (9, 75).

Sites must be prepared in advance to address several study-related issues, such as: the recruitment process, the informed consent process; inclusion/exclusion criteria; disease issues; protocol review; training, GPC. At the same time, a visit to the site facilities is very likely to occur. It will probably include examination rooms, laboratories, pharmacy, site staff work area and storage areas (study drug, supplies and source documentation)(75).

Inspections findings can be classified in 3 different ways. The most frequent findings on EMA inspections between 2000 and 2012 will be outlined in the tables below.

Critical: "Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data". These findings are considered totally unacceptable, since they represent a significant risk and pattern of deviation that can lead to data rejection and/or legal actions.

Major: "Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data". These observations are serious findings and result from a direct violation of GCP principles and will likely include a pattern of deviation and/or various minor observations. Some of the possible consequences are data rejection and in some cases legal action.

Minor: "Conditions, practices or processes that would not be expected to adversely affect the right, safety or well-being of the subjects and/or the quality and integrity of data". Minor findings suggest the need to improve processes, practices and conditions. A number of minor finding can become a major finding (106).

Finding sub-category name	No.	% *	% **
Monitoring	49	9.2%	0.9%
Data management	48	9.0%	0.8%
Clinical Study Report	47	8.8%	0.8%
Protocol compliance (selectioncriteria)	33	6.2%	0.6%
Source documentation	32	6.0%	0.6%
Protocol compliance (assessment of efficacy)	23	4.3%	0.4%
Protocol/CRF/diary/questionnaires design	21	3.9%	0.4%
IMP accountability	20	3.8%	0.4%
Protocol compliance (safetyreporting)	19	3.6%	0.3%
Prescription/administration/compliance	18	3.4%	0.3%
Reporting in CRF/diary	18	3.4%	0.3%
Grand total	**328**	**61.6%**	**5.8%**

*Related to the total number of critical findings (No. = 532) **Related to the total number of findings (No. = 5685)

Table 3 - EMA Ranking of the top 10 critical GCP findings (2000-12) (adapted from (106))

Finding sub-category name	No.	% *	% **
Monitoring	187	7.2%	3.3%
Source documentation	180	7.0%	3.2%
Data management	176	6.8%	3.1%
Supplying/storage/retrieving/destruction	138	5.3%	2.4%
Protocolcompliance(selectioncriteria)	131	5.1%	2.3%
Essentialdocuments	130	5.0%	2.3%
Reporting in CRF/diary	130	5.0%	2.3%
SOPs	127	4.9%	2.2%
Qualification/training	121	4.7%	2.1%
Clinical Study Report	94	3.6%	1.7%
Grand total	**1414**	**54.7%**	**24.9%**

* Related to the total number of major findings (No. = 2583) ** Related to the total number of findings (No. = 5685)

Table 4 - EMA Ranking of the top 10 major GCP findings (2000-12) (adapted from(106))

Finding sub-category name	No.	% *	% **
Essential documents	322	12.5%	5.7%
Reporting in CRF/diary	200	7.8%	3.5%
Source documentation	160	6.2%	2.8%
Organisation and personnel	158	6.1%	2.8%
Qualification/training	134	5.2%	2.4%
Supplying/storage/retrieving/destruction	126	4.9%	2.2%
SOPs	117	4.6%	2.1%
Monitoring	108	4.2%	1.9%
Document control	95	3.7%	1.7%
Data management	92	3.6%	1.6%
Grand total	**1512**	**58.8%**	**26.7%**

Related to the total number of minor findings (No. = 2570) **Related to the total number of findings (No. = 5685)

Table 5 - EMA Ranking of the top 10 minor GCP findings (2000-12) (adapted from (106))

6.6.3. Trial Closure

After its completion, every study must be closed out at investigative sites. In normal circumstances, this occurs when all subjects have completed study related activities and data verification is completed. However, trials can end earlier due to unfavorable reasons such as safety or efficacy issues associated with the investigational drug, insufficient enrolment or any other problems with site's compliance or marketing issues. When there is a decision to close a site, the CRA will conduct a close-out visit which will be focused on four main aspects: CRF, Study Drug accountability, ISF and other administrative issues related with the close-out (9).

In accordance with ICH Topic E6 R1 "Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial outcome, and the regulatory authority(ies) with any reports required" (92).

Another important aspect relates to record retention. Regulations state that "sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region" (92).

However, sponsors expect that Investigators retain trial recordings for a much longer period of time than that they are legally obligated to. Frequently, this information is stated in the agreement signed between both parties before the study starts (9).

6.6.3.1. Post-Study Critique

Post-Study Critique is a meeting that includes all site investigational team and occurs after trial closure. Before this meeting takes place, PI and CRC are to compile a summary of trial related data that should include the number of participants (screened, enrolled and completing), site achieved timelines, site safety information (AE, SAE and other related issues), protocol deviation, problems found and other constraints and relevant information. It is also advisable that a financial analysis takes place in order to understand if it was feasible to participate in the study. This summary should be sent to the entire team before the meeting. During the meeting, the Investigational team should carefully and openly discuss all that did and did not go well throughout study implementation. This evaluation should be kept by the site in order to be used as a guiding document for future studies (9).

7. Discussion

As demonstrated thorough this project, developing new and improved treatments for diseases that affect millions of people worldwide highly depends on the safe and competent conduct of clinical research. Because clinical research is mainly focused in discovering beneficial effects and/or assessing safety and efficacy of new or existing medicines it is crucial to obtain quality data. Since this data will be on the basis of a regulatory approval for a marketing authorization, there is a real need to improve the way clinical trials are designed, conducted and reported (9, 75).

This project focused on a clinical trial conduction at an investigative site and particularly on the CRC importance to that process. Before discussing in a detailed way the relevance of this professional in the conduct of a clinical trial in a rare disease I will analyze some of the relevant literature findings.

One of the aspects that was consensual throughout literature search on the state-of-the art was the fact that developing a new drug is a long and highly complex process where the results are uncertain for a long period of time. Costs associated with the discovery and development of a single new drug have increased and can now exceed 2 billion dollars. At the same time, despite the huge investment being done on R&D, there is a substantial decline in the number of new drugs that achieve market phase. Indeed, it seems unequivocal that the current R&D model is going through difficult and decisive moments and the adoption of a new paradigm urges.(4, 35)

Finding proof of concept early in the drug development pipeline is essential. Concomitantly, there is a real need to adopt strategies based on innovation and that make use of “Omnic” research and personalized medicine (34, 35, 47). At the same time, addressing unmet medical needs, where value can be more easily demonstrated, is another way pointed by authors to reverse the current paradigm. This is well reflected in the incentives and initiatives related with orphan drugs implemented worldwide by regulatory authorities. A good example of this trend, and proven by this project, is the substantial increase of pharmaceutical company’s investment in a rare disease such as FAP and other amyloid related diseases. However, it should be noted that prices for new and innovative drugs for

rare diseases are becoming an important issue and there is an effective need to address this sensitive matter without compromising patient access to those medicines (35, 58, 62).

Also it became clear that R&D of new drugs involves a number of stakeholders and any attempt to be successful lies on the synergy of knowledge, perspectives and forces that often seem conflicting(35).

Regarding CRCs it was found that they play a very relevant role in clinical research. Despite some lack of awareness to this fact, a well-trained CRC can contribute to the achievement and maintenance of the highest ethical standards, ensure data integrity and study participant's safety. This clearly puts them at the center of research process with the capability to influence the integrity and to some extent the outcomes of the research. One of the most relevant indicators of this importance is the fact that an increasing number of sponsors require the existence of full time dedicated CRCs at the investigative sites where they decide to conduct trials. Despite obvious, for many years this role was partially assured by site staff with limited time and experience and not so often without proper qualifications (9, 75). In my opinion, and based on recent experience, this reality is slowly changing and nowadays we see that institutions who conduct clinical research are requiring professionals with a background on sciences, formal training and/or previous professional experience or internships in clinical research activities. This is also based upon the notion that coordinating clinical research is a highly demanding task that requires full time, dedicated jobs and the capacity to handle a different number of knowledge domains that range from ethical, technical, clinical and regulatory (9, 75).

Nonetheless, it is important to state that job satisfaction needs to be nurtured at the research site and opportunities for growth and professional development created. As outlined by some authors, avoiding frequent turnovers on this job can be obtained by increasing salary levels, improving benefits packages, flexible hours, hiring of additional staff to assist in study specific activities and creating opportunities for promotions and career advancement (75).

Because the context is fundamental to understand the current reality, literature indicates that there are still a number of constrains with a negative impact on the daily dynamic of

clinical research in our country. As noted in the report on clinical trials in Portugal, issues ranging from inadequate infrastructures and supra-structures, to an outdated regulatory framework and the lack of awareness of the importance of clinical trials by the hospital administrations, are still obstacles to the full development of this activity. This is somehow difficult to understand when there is increasing evidence that the development of clinical research in hospitals is a differentiation factor that includes numerous advantages. These can be of economic type, through the caption of the funds inherent to the inclusion of participants, or purely of medical type, through the possibility of offering treatment alternatives to patients who would not have them outside of the research context and the possibility to improve medical practice as a result of assimilation of research methods in clinical practice (20, 21, 49).

In what concerns the implementation of this project, I would like to point that coordinating very complex protocols such as ISIS420915-CS2 and ISIS420915-CS3 in a severe disease like FAP requires very good organizational skills and also the capability to deal with highly stressful situations and constant unforeseen circumstances. In this sense I would like to stress the importance of the Masters theoretical component in my daily practice. Because protocols are increasingly complex in clinical trials for rare diseases and patient population is often scarce, a good understanding of clinical research and clinical trial protocol designs has proven to be crucial and has helped me dealing in a more effective way with daily constrains. Also, and has it will be demonstrated, the successful conduction of clinical trials is highly dependent on site's organization and on the study team previous experience in conducting clinical trials.

As mentioned before, UCA has been intensively developing clinical research over the past ten years. Despite having as primary goal the treatment of FAP patients, UCA represents a very important research center within the CHP. Following the largest number of patients with FAP in the world, it is a fundamental site for any clinical trial that is to be conducted with this population. This, along with the UCA director's vision and dedication, have allowed for the creation of a local clinical research structure that includes several CRC, working on a full time basis, a dedicated team of investigators with experience on FAP and

clinical research, and facilities and resources to fully develop research. It should be noted that the first approved medicine to treat FAP was the result of a core registration clinical trial whose main enroller was UCA.

In this sense, and to better understand how a proper setting is essential to an effective conduct of a clinical trial, I will now outline some of the benefits and also some of the constraints that I have experienced during the implementation and conduct of this project.

Because everything starts with patients, the fact that UCA has a large patient database with a very well characterized population represents a major tool to select potential patients to enroll, therefore reducing the number of screen failures and resource consumption inherent to it. This also allows for a more realistic estimate of the number of patients that can be enrolled, contributing to achieve the study's goals. Since UCA resources, including examination rooms, nursing room, laboratories, PI, CRC and monitors working offices are all gathered in the same building, everything becomes more practical and doable in terms of trial conduct and protocol compliance. This facilitates the communication between Investigators, CRCs and CRAs, which is a crucial element to proper conduction of clinical research. This is also very important for patients, who can perform almost every study visit in the same place, avoiding the burden of going through several departments to conduct a trial visit. Also, another positive aspect of working for so many years in this unit with trials and studies dedicated to FAP is that I have gained a profound knowledge of the target disease. This is very relevant in terms of protocol comprehension, AE monitoring/reporting and data management. At the same time, there is an underlying satisfaction that results from knowing I'm actively contributing to address an unmet medical need in such a severe disease.

In terms of trial conduction, given the high number of enrolled patients, procedures, and the duration of the study, it was obvious from an early stage that the only way to ensure proper compliance with the protocol would depend on my total allocation to this project. It was also clear from the outset of the study the research team commitment to this endeavor. Of the 20 team members that are currently participating, there was always a collaborative environment with positive impact on study conduct. One of the aspects that

makes the coordination of this trial particularly demanding has to do with the type of patients recruited, many of them in an advanced stage of disease. Besides the obvious motor and dysautonomic difficulties related with the disease, these patients have a higher number of AEs when compared with early stages patients. Indeed, one of the greatest challenges relates to the management of safety issues. With tight analytical criteria, including various safety/stopping rules for various physical systems, there have been constant contacts between the site and sponsor's medical monitors in order to discuss the various complications and ensure that safety procedures outlined in protocol and regulations were strictly met.

Due to the fact that UCA recruited a significant number of patients and also considering that this is a core registration study, I was aware from the beginning that this site could be a potential target for a regulatory inspection. Actually, UCA was first audited by the sponsor after enrolling the first patients in anticipation of an inspection. It was a routine GCP audit and it revealed to be very important to improve and correct some aspects that could represent potential findings during an Inspection. As anticipated UCA came to be inspected by INFARMED one year later. This was a very demanding experience but it turned out with a very positive outcome and inspectors considered ours to be a highly organized and compliant site. This has proven to be a very constructive experience and the major lesson I learnt is that the best way to deal with audits/inspections is to comply with GCP and protocol on a daily basis.

Despite this research-friendly environment, in my opinion there are some things that can be improved. As stated before, drug development is a highly demanding, complex and regulated activity. This poses a major challenge to investigative sites involved in the process, requiring highly organized process and procedures. At this level, I believe that it would be beneficial for UCA to create internal Standard Operating Procedures (SOPs) that would contribute to the harmonization of procedures, increasing compliance and adherence to GCP. At the same time, I believe that implementing periodic training in clinical research for all team members would largely contribute to a culture of high standard practice.

At an institutional level, despite the fact that the number of trials has been increasing in CHP in recent years (from 66 in 2013 to 84 in 2014) and the obvious awareness of the fact that clinical research is a highly strategic sector for the hospital, in my opinion, there is still a long road ahead and the hospital could benefit if there was an integrated growth strategy for clinical research that could address many issues that are related with the scarcity of adequate physical and human resources, training and incentives for conducting clinical research.

8. Conclusion

Developing this project was a very challenging and positive experience. From the first moment there were three main goals that I wanted to accomplish.

Firstly, I wanted to systemize the knowledge acquired during the Masters in Pharmaceutical Medicine and frame it on my daily work as a CRC. It had become evident throughout the Masters' theoretical component that a good theoretical basis enhances proper practical application of knowledge and leads to a more effective embodiment of daily work and challenges. This assumes more relevance when we are dealing with a field of knowledge such as Pharmaceutical Medicine, where regulations, guidelines and procedures proliferate and are in constant change.

Secondly, I wanted to contribute to minimize what I consider to be a gap in clinical research literature that is the unavailability of specific literature on the coordination of clinical trials and clinical research. Despite the specificity of the study and setting, I believe that this project might be regarded as an introductory guide for those who wish to learn more about clinical trial coordination and access the perspective of someone who has been in the field for nearly 8 years. Also, despite some recent positive examples in our country, where the Pharmaceutical Training Program of the University of Aveiro is a good example, this literature gap is unprecedented and goes along with very little quality training opportunities available, either for experienced CRCs or anyone who intends to start working on clinical research coordination.

Finally, I wanted this project to represent a serious reflection on my professional experience as CRC, allowing me to identify difficulties, challenges and areas for improvement that ultimately could translate into a real benefit to my work and those with whom I have the opportunity to learn and work.

Now that I am close to finish this important stage of my academic life, I can say with conviction that all three initial goals are very near to be accomplished and that the opportunity to carry out the Master's was a decisive moment in my career. In addition to giving me a solid training on Pharmaceutical Medicine, it also provided me with a set of

essential tools and knowledge to use in the future, whether as a CRC or as a professional in one of the many roles within clinical research.

Despite the enormous challenge that was to reconcile professional and academic life for almost three years, this course turned out to be a very rewarding experience and an amazing learning opportunity with a very tangible impact in the quality of my daily work.

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